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Anesthesia and Analgesia

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Journal of the International Anesthesia Research Society
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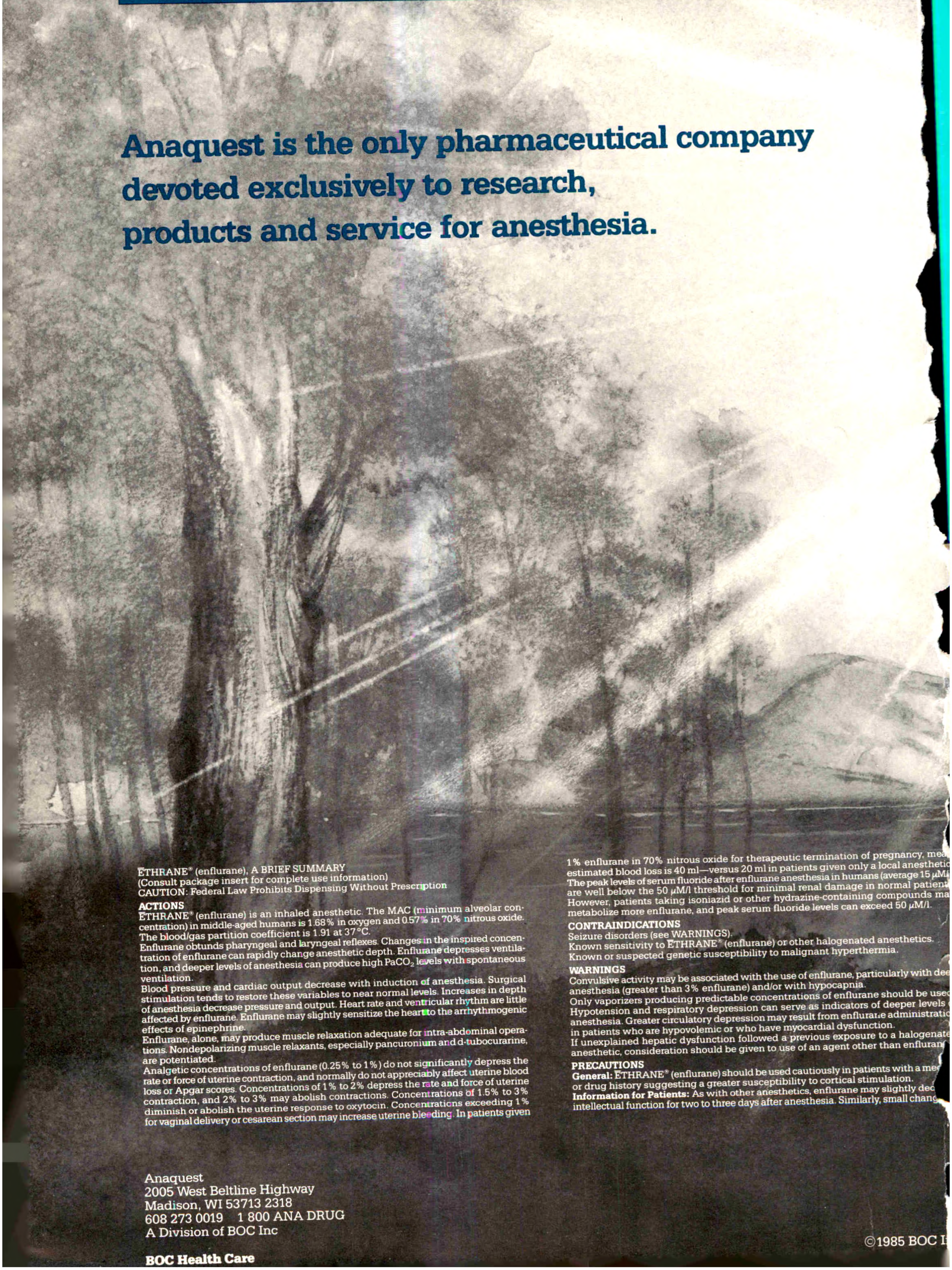

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ETHRANE® (enflurane), A BRIEF SUMMARY
(Consult package insert for complete use information)
CAUTION: Federal Law Prohibits Dispensing Without Prescription

ACTIONS
ETHRANE® (enflurane) is an inhaled anesthetic. The MAC (minimum alveolar con-
centration) in middle-aged humans is 1.68% in oxygen and 0.57% in 70% nitrous oxide.
The blood/gas partition coefficient is 1.91 at 37°C.
Enflurane obtunds pharyngeal and laryngeal reflexes. Changes in the inspired concen-
tration of enflurane can rapidly change anesthetic depth. Enflurane depresses ventila-
tion, and deeper levels of anesthesia can produce high $PaCO_2$ levels with spontaneous
ventilation.
Blood pressure and cardiac output decrease with induction of anesthesia. Surgical
stimulation tends to restore these variables to near normal levels. Increases in depth
of anesthesia decrease pressure and output. Heart rate and ventricular rhythm are little
affected by enflurane. Enflurane may slightly sensitize the heart to the arrhythmogenic
effects of epinephrine.
Enflurane, alone, may produce muscle relaxation adequate for intra-abdominal opera-
tions. Nondepolarizing muscle relaxants, especially pancuronium and d-tubocurarine,
are potentiated.
Analgetic concentrations of enflurane (0.25% to 1%) do not significantly depress the
rate or force of uterine contraction, and normally do not appreciably affect uterine blood
loss or Apgar scores. Concentrations of 1% to 2% depress the rate and force of uterine
contraction, and 2% to 3% may abolish contractions. Concentrations of 1.5% to 3%
diminish or abolish the uterine response to oxytocin. Concentrations exceeding 1%
for vaginal delivery or cesarean section may increase uterine bleeding. In patients given
1% enflurane in 70% nitrous oxide for therapeutic termination of pregnancy, mea
estimated blood loss is 40 ml—versus 20 ml in patients given only a local anesthetic
The peak levels of serum fluoride after enflurane anesthesia in humans (average 15 μM
are well below the 50 μM/l threshold for minimal renal damage in normal patient
However, patients taking isoniazid or other hydrazine-containing compounds ma
metabolize more enflurane, and peak serum fluoride levels can exceed 50 μM/l.

CONTRAINDICATIONS
Seizure disorders (see WARNINGS).
Known sensitivity to ETHRANE® (enflurane) or other halogenated anesthetics.
Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS
Convulsive activity may be associated with the use of enflurane, particularly with dee
anesthesia (greater than 3% enflurane) and/or with hypocapnia.
Only vaporizers producing predictable concentrations of enflurane should be use
Hypotension and respiratory depression can serve as indicators of deeper levels
anesthesia. Greater circulatory depression may result from enflurane administratio
in patients who are hypovolemic or who have myocardial dysfunction.
If unexplained hepatic dysfunction followed a previous exposure to a halogenate
anesthetic, consideration should be given to use of an agent other than enfluran

PRECAUTIONS
General: ETHRANE® (enflurane) should be used cautiously in patients with a me
or drug history suggesting a greater susceptibility to cortical stimulation.
Information for Patients: As with other anesthetics, enflurane may slightly dec
intellectual function for two to three days after anesthesia. Similarly, small chang

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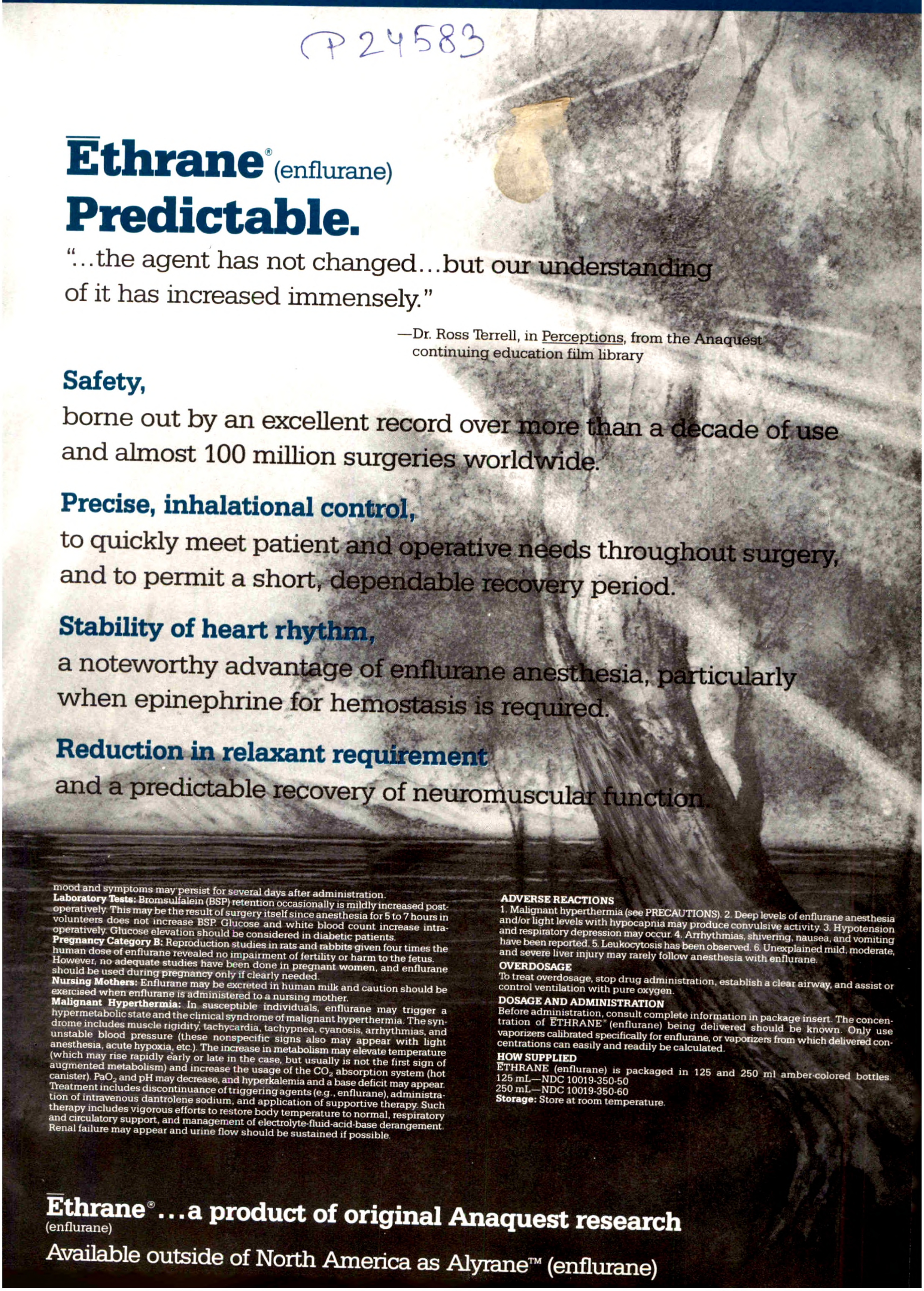

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Stability of heart rhythm,

a noteworthy advantage of enflurane anesthesia, particularly when epinephrine for hemostasis is required.

Reduction in relaxant requirement

and a predictable recovery of neuromuscular function.

mood and symptoms may persist for several days after administration.

Laboratory Tests: Bromsulfalein (BSP) retention occasionally is mildly increased postoperatively. This may be the result of surgery itself since anesthesia for 5 to 7 hours in volunteers does not increase BSP. Glucose and white blood count increase intraoperatively. Glucose elevation should be considered in diabetic patients.

Pregnancy Category B: Reproduction studies in rats and rabbits given four times the human dose of enflurane revealed no impairment of fertility or harm to the fetus. However, no adequate studies have been done in pregnant women, and enflurane should be used during pregnancy only if clearly needed.

Nursing Mothers: Enflurane may be excreted in human milk and caution should be exercised when enflurane is administered to a nursing mother.

Malignant Hyperthermia: In susceptible individuals, enflurane may trigger a hypermetabolic state and the clinical syndrome of malignant hyperthermia. The syndrome includes muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure (these nonspecific signs also may appear with light anesthesia, acute hypoxia, etc.). The increase in metabolism may elevate temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and increase the usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., enflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support, and management of electrolyte-fluid-acid-base derangement. Renal failure may appear and urine flow should be sustained if possible.

ADVERSE REACTIONS

1. Malignant hyperthermia (see PRECAUTIONS). 2. Deep levels of enflurane anesthesia and/or light levels with hypocapnia may produce convulsive activity. 3. Hypotension and respiratory depression may occur. 4. Arrhythmias, shivering, nausea, and vomiting have been reported. 5. Leukocytosis has been observed. 6. Unexplained mild, moderate, and severe liver injury may rarely follow anesthesia with enflurane.

OVERDOSAGE

To treat overdosage, stop drug administration, establish a clear airway, and assist or control ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

Before administration, consult complete information in package insert. The concentration of ETHRANE® (enflurane) being delivered should be known. Only use vaporizers calibrated specifically for enflurane, or vaporizers from which delivered concentrations can easily and readily be calculated.

HOW SUPPLIED

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125 mL—NDC 10019-350-50

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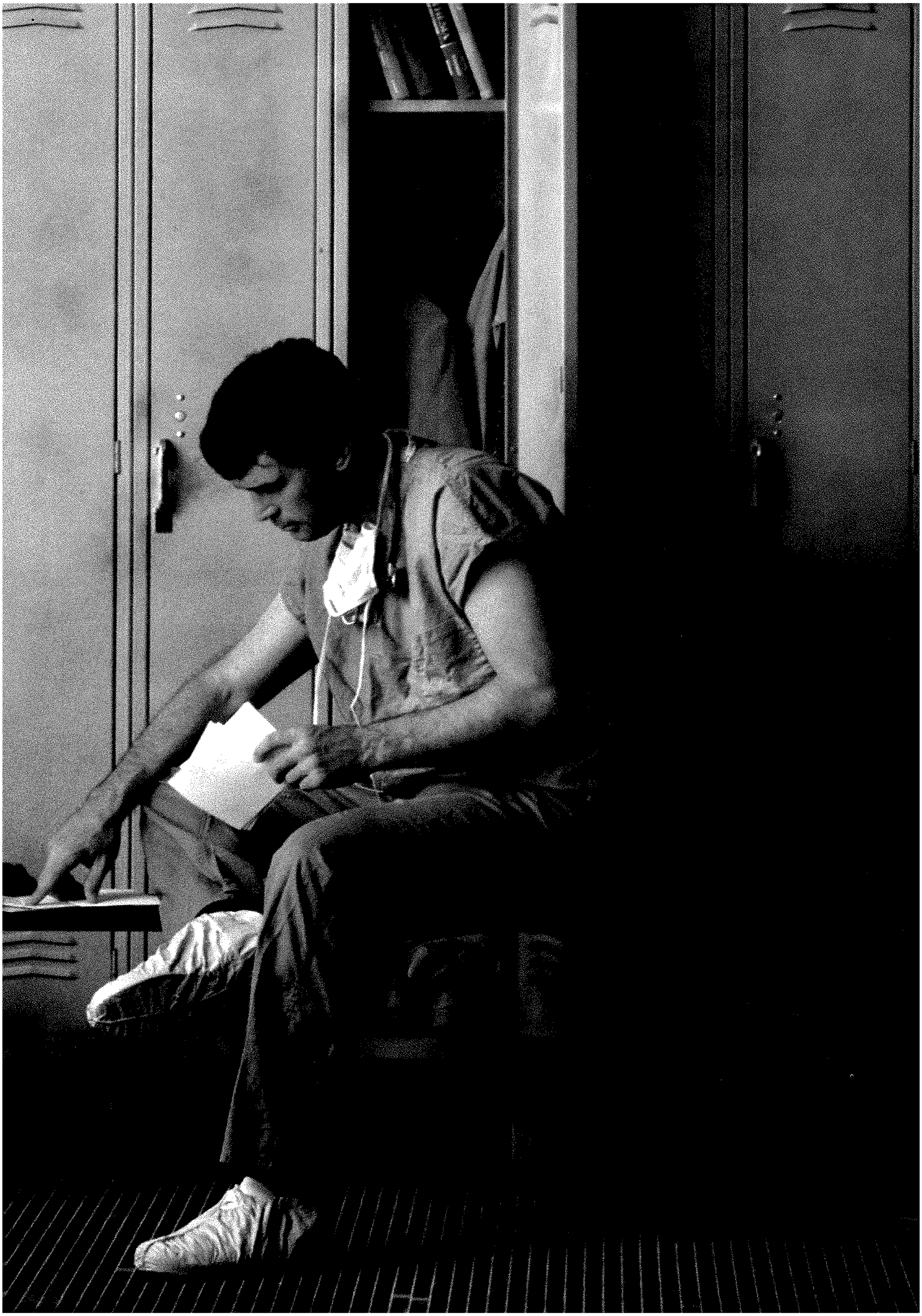

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REFERENCES
1. Pierce HE: An effective method of inducing analgesia and anesthesia for dermatoplastic surgery in an office. J Dermatol Surg Oncol *1981;7:495-498./2. Cook TA: Butorphanol tartrate: An intravenous analgesic for outpatient surgery.* Otolaryngol Head Neck Surg *1983;9:251-254./3. Kallos T, Caruso FS: Respiratory effects of butorphanol and pethidine.* Anaesthesia *1979;34:633-637./4. Skaredoff MN, Viguera MG: Double-blind comparison of butorphanol and morphine in balanced anesthesia.* Anesthesiology Review *1980;7(No. 10):36-39.*

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CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.
WARNINGS—Patients Physically Dependent on Narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.
Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.
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PRECAUTIONS—Certain Respiratory Conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.
Impaired Renal or Hepatic Function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.
Biliary Surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.
Usage as a Preoperative or Preanesthetic Medication: Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.
Usage in Balanced Anesthesia: The use of pancuronium in combination with Stadol may cause an increase in conjunctival changes.
Usage in Pregnancy: The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient. Reproduction studies have been performed in rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.
Usage in Labor and Delivery: Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.
Usage in Nursing Mothers: The use of Stadol in lactating mothers who are nursing their infants is not recommended since it is not known whether this drug is excreted in human milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.
Usage in Children: Safety and efficacy in children below age 18 years have not been established.
ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).
Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).
Other adverse reactions which may occur (reported incidence of less than 1%) are:
CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations
Autonomic: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision
OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.
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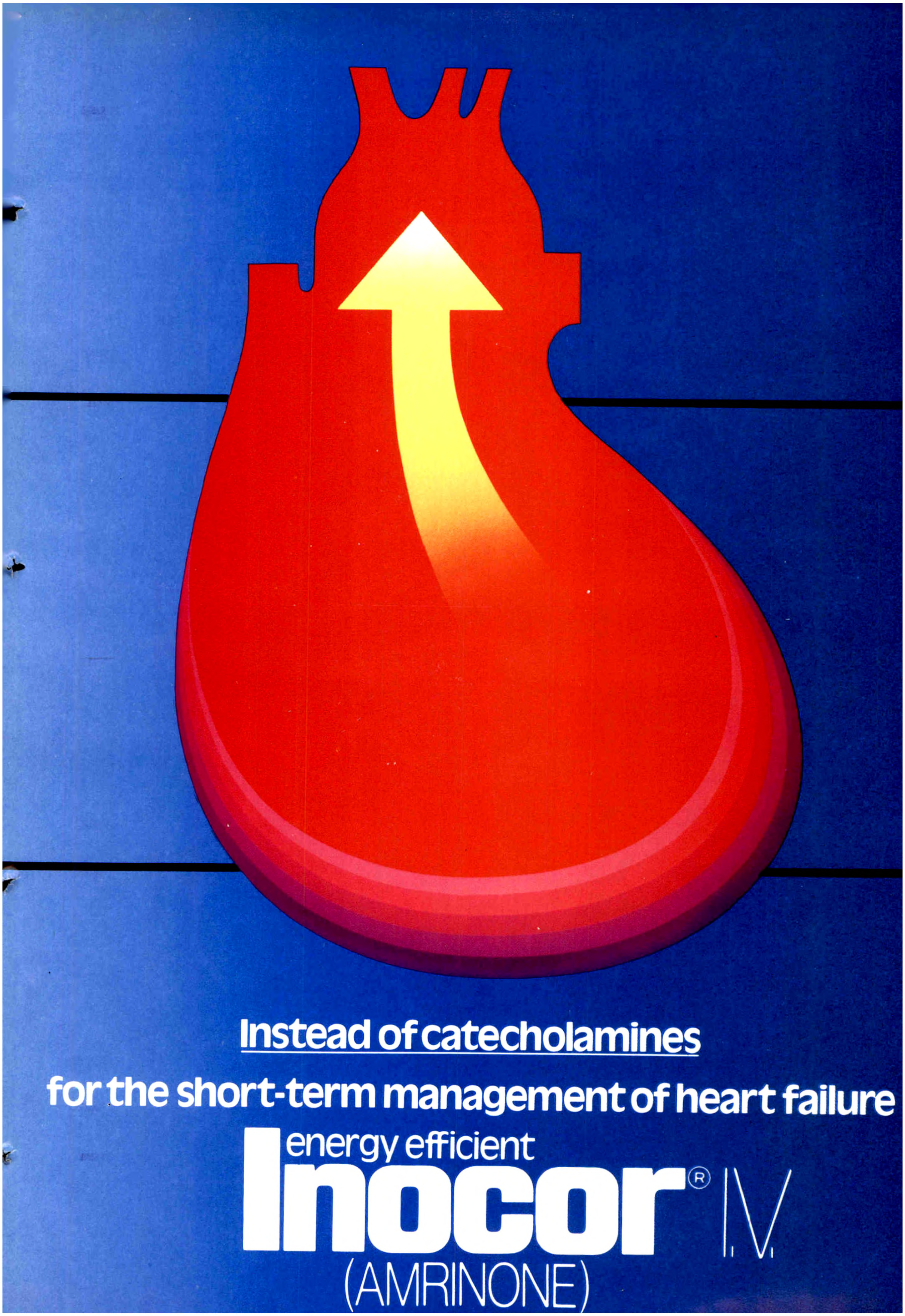
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(AMRINONE)

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- Can be used in patients with myocardial ischemia
- Benefits sustained during therapy... no evidence of tachyphylaxis
- Easy to administer

Patients receiving INOCOR should be carefully monitored with the following laboratory studies: platelet counts, liver enzymes, fluid and electrolyte changes, and renal function. Hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

1. Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. *Circulation* 1980;62:28-34.

Please see brief summary of product information on this page for contraindications, adverse reactions, patient selection, and precautionary recommendations.

Winthrop-Breon

Winthrop-Breon Laboratories, Division of Sterling Drug Inc., New York, NY 10016

61065

INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General:* INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes:* Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol; hydralazine, prazosin, isosorbide dinitrate, nitroglycerine; chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established

USE IN PREGNANCY *Pregnancy category C:* In New Zealand white rabbits, amrinone has been shown to reduce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia:* Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm^3 in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case); myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone

General: Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions:* Asymptomatic platelet count reduction (to less than 150,000/mm^3) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications.

Should a platelet count less than 150,000/mm^3 occur, the following actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepatotoxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amrinone therapy should be promptly discontinued

If less than marked enzyme alterations occur without clinical symptoms, these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amrinone and reduce the dosage or discontinue the drug based on the usual benefit-to-risk considerations.

HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containing INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR lactate equivalent to 5-mg base and 0.25 mg sodium metabisulfite in water for injection

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
60th CONGRESS—March 15–19, 1986—
Caesars Palace Hotel, Las Vegas, Nevada

PRELIMINARY MEETING INFORMATION

Program/Registration Mailing: The preliminary program, with daily schedule of presentations, will be sent out in mid-December to all IARS members. This will include registration card, hotel card, social activities and spouse program. (IARS members outside of North America who plan to attend the meeting can receive this material by airmail upon request.) Non-IARS members who wish to receive meeting/membership information should contact the Cleveland office.

Schedule:	Registration: Saturday, March 15—1–5 PM (continues daily) Scientific Program: Sunday, March 16, through Wednesday, March 19 Exhibits: Sunday, March 16, through Tuesday, March 18
Program:	• T.H. Seldon Distinguished Lecture—Dr. J. Alfred Lee, Essex, England • 26 Review Course Lectures • Panels: Outpatient Anesthesia, Cardiovascular Anesthesia • Over 100 Scientific Papers • Scientific Poster Presentations • Theme Luncheon Sessions • Scientific Exhibits
Technical (Commercial) Exhibits:	Including a number of company sponsored Product Seminars
Spouse Program:	"Effective Tax Strategies" Seminar; area tours and other activities and presentations of interest.
Reduced Air Fare:	A special discounted fare will be available through United Airlines for IARS registrants.
CME Credit:	AMA/ACCME Category 1 (31 hr, est.) AANA credit to be confirmed.

SCIENTIFIC EXHIBITS: Applications for scientific exhibit space are available from the IARS office. There is no absolute deadline for submission of applications. However, availability of space in the exhibit area will be a factor in considering applications received after January 1, 1986.

ARTS AND CRAFTS EXHIBIT: Responding to interest expressed by a number of members, the IARS will for the first time include an arts and crafts exhibit at the 1986 meeting. If you or your spouse would like to enter your personally done art or craft work, the rules and entry blanks are available from the Cleveland office. **The deadline for entry is January 31, 1986.**

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CONTRAINDICATIONS
Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

WARNINGS
Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.
Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.
Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.
Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.
Usage in Children: No data available pertaining to use in children.
The safety and compatibility of additives have not been established.

PRECAUTIONS
The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.
Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).
Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

ADVERSE REACTIONS
The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

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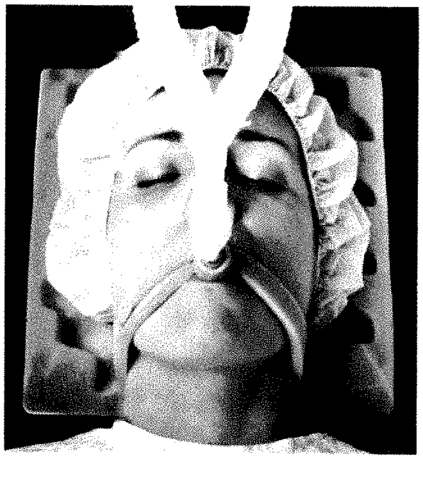

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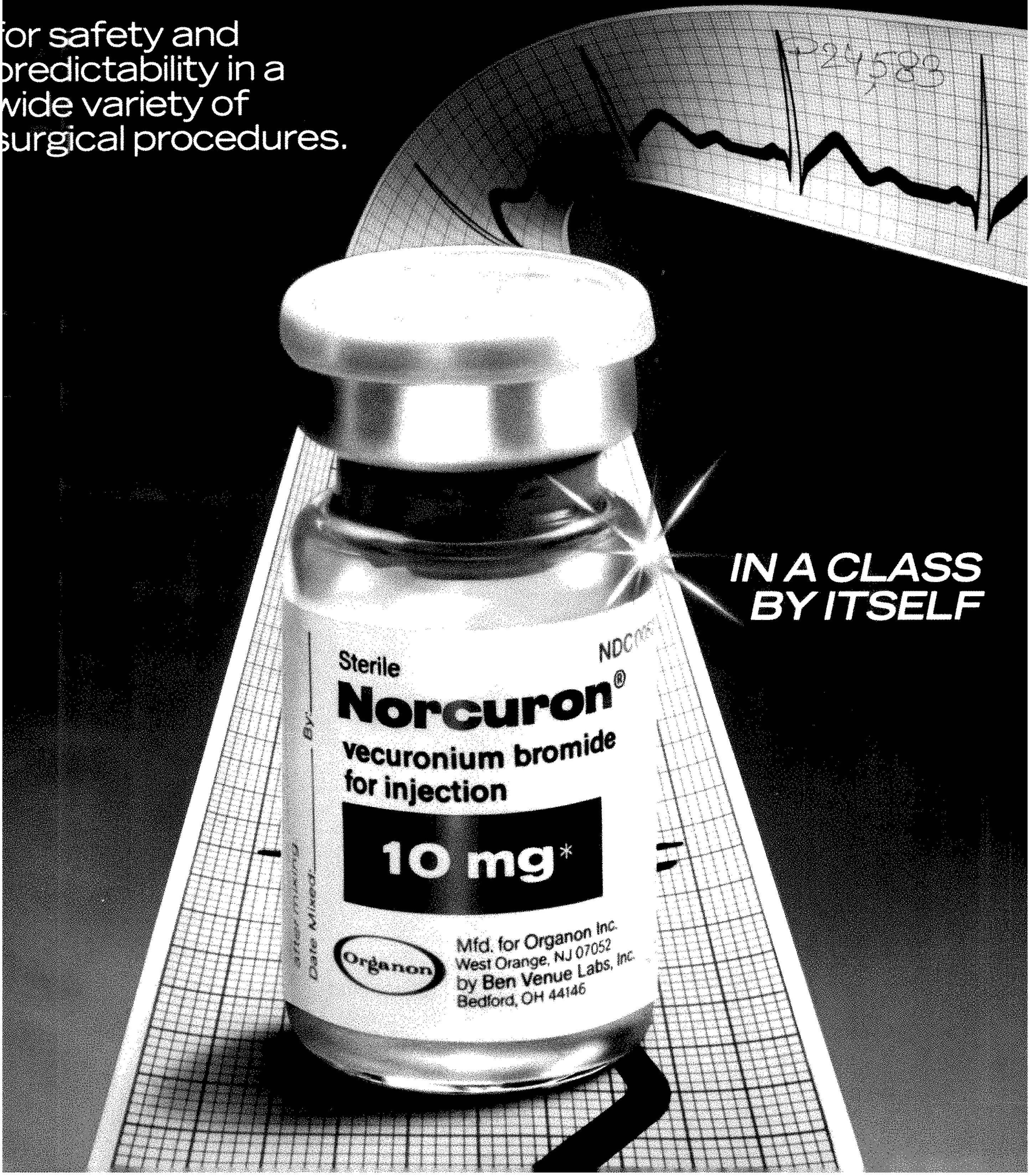

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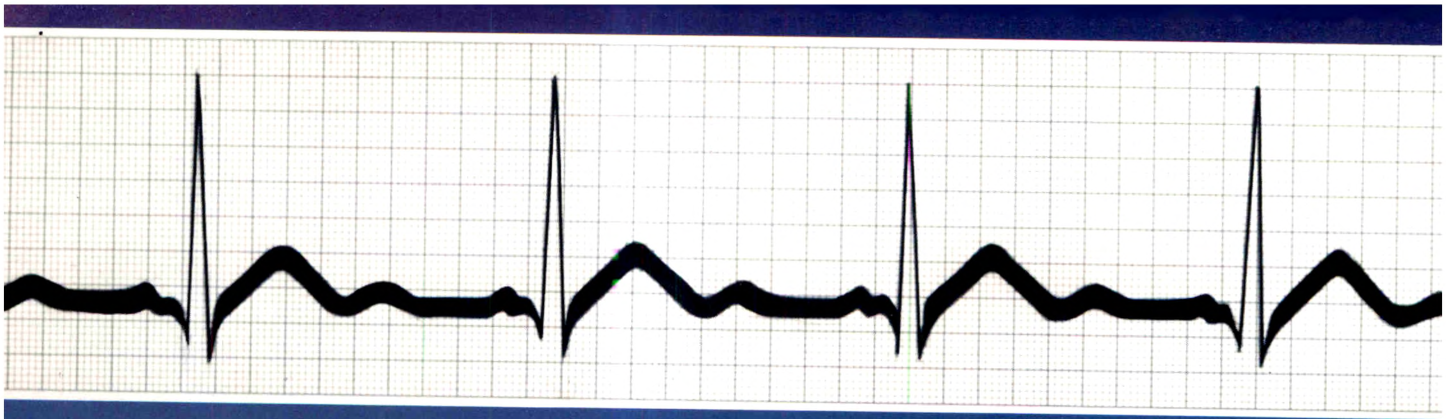

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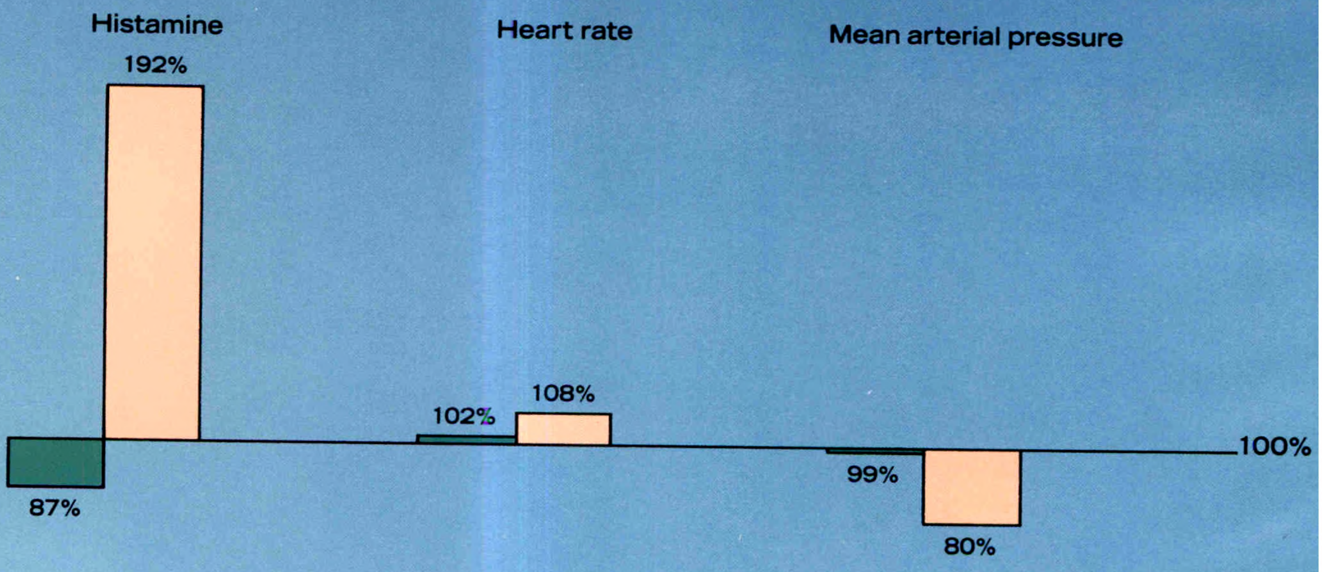
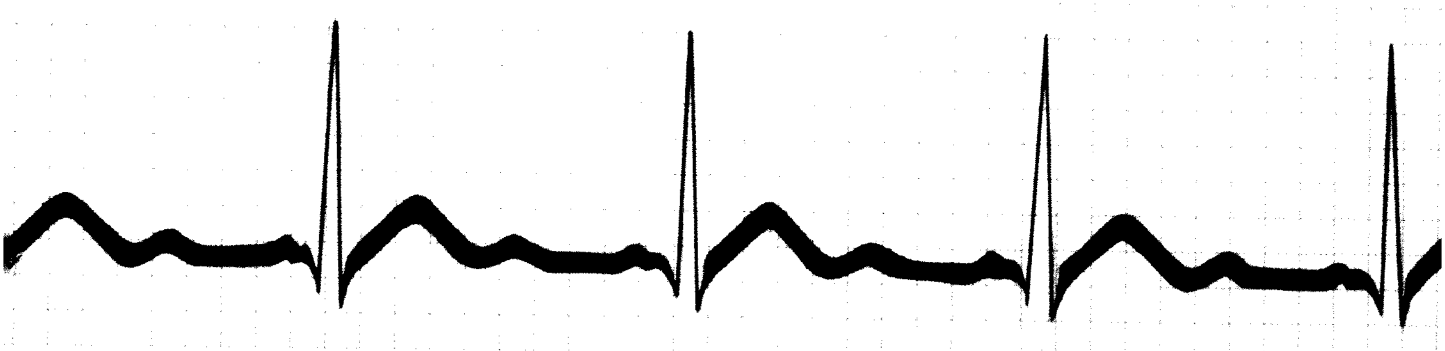
☐ indicated for patients with underlying cardiovascular problems undergoing various surgical procedures

Histamine release unlikely to occur[5]



	Drug	Dose (mg/kg)	n	$\times ED_{95}$
🟧	Atracurium	0.6	10	3
🟩	Vecuronium	0.2	8	3.5



For predictability

☐ may be used alone for intubation within 2½ to 3 minutes
☐ lacks clinically important cumulative effects

Indicated for:

☐ procedures lasting 25 minutes or longer
☐ the patient with asthma
☐ outpatient surgery
☐ pediatrics (infants seven weeks or older)

Before you decide, consider:

NORCURON® (vecuronium bromide) injection	
Histamine release	unlikely to occur
Cardiovascular effects	none clinically significant
Refrigeration	not required; stable at room temperature
Potency	reliably activated upon demand
Metabolites	3-deacetyl vecuronium
Usage in infancy	yes: seven weeks or older

NORCURON®

IN A CLASS BY ITSELF

References 1. Morris RB, Cahalan MK, Miller RD, et al: The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 58:438-440, 1983. 2. Krieg N, Crul JF, Booij LH: Relative potency of ORG NC45, pancuronium, alcuronium and tubocurarine in anaesthetized man. *Br J Anaesth* 52:783-788, 1980. 3. Lienhart A, Guggiari M, Maneglia R, et al: Cardiovascular effects of vecuronium in man, in Agoston S et al (eds): *Clinical Experiences with Norcuron® (Org NC 45, Vecuronium Bromide)* (Symposium Geneva, 21-22 April, 1983). Current Clinical Practice Series 11, Amsterdam, Excerpta Medica, 1983, pp 150-155. 4. Gallo JA, Fries E, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 61:A63, 1984. 5. Basta SJ, Savarese JJ, Ali HH, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 59:A273, 1983.

NORCURON®

(vecuronium bromide injection)

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide injection) is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2 β, 3α, 5α, 16β, 17β)-3,17-bis(acetyloxy)-2-(1-piperidinyl)-androstan-16-yl]-1-methyl-, bromide. The structural formula is:

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide injection) is a nondepolarizing neuromusular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45–65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04–0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25–30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15–25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04–0.10 mg/kg, 60–80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025–0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65–75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35–40 minutes. The volume of distribution at steady state is approximately 300–400 ml/kg; systemic rate of clearance is approximately 3–4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3–35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25–50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide injection) has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

NO
REFRIGERATION
REQUIRED

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide injection) and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04–0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25–30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in th
fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. Th
insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcurc
enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above age
initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administe
a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neurom
block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (s
neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colis
sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during s
unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that re
paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular block
been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and disease
lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. De
on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered
management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to
carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also no
whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. No
should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderate
sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently
does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. T
frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharma
action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profo
prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all cu
drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Lit
increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic an
nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which als
respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage
minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular
beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular block
may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripher
stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuron
blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia
narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary trea
maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is
Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrr
usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy o
muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to
restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the pre
extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum a
or anesthetic agents and other drugs which enhance neuromuscular blockade or cause re
depression of their own. Under such circumstances the management is the same as that of p
neuromuscular blockade. Ventilation must be supported by artificial means until the pa
resumed control of his respiration. Prior to the use of reversal agents, reference should be ma
specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide injection) is for intrave
only. This drug should be administered by or under the supervision of experienced clinician
with the use of neuromuscular blocking agents. Dosage must be individualized in each case. Th
information which follows is derived from studies based upon units of drug per unit of body wei
intended to serve as a guide only, especially regarding enhancement of neuromuscular bl
Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Dru
tions). Parenteral drug products should be inspected visually for particulate matter and dis
prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdo
monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intraven
injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 min
injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25–30 minu
recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control
approximately 45–65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular block
of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or wh
state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Nor
intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04–0.06 mg/kg with i
anesthesia and 0.05–0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended;
initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinic
should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulativ
subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient
approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less
administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg
mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular sys
noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg)
and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose an
require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moder
sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also sub
PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neo
PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:
0.9% NaCl solution
5% glucose in water
5% glucos
Lactat

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for i
the diluent.
Boxes of 12. NDC# 0052-0442-10

STORAGE: PROTECT FROM LIGHT. Store at 15°–30°C (59°–86°F)

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30
DISCARD SOLUTION AFTER 24 HOURS.

DISCARD UNUSED PORTION.

SINGLE U

PTD. IN USA-442

ISSUE

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ANESTH ANALG
1986;65:1–8

Active Inspiratory Impedance and Load Compensation:

Effects of Duration of Anesthesia

Ahmet Baydur, MD, Catherine S. H. Sassoon, MD, and Claire M. Stiles, MD

BAYDUR A, SASSOON CSH, STILES CM. Active inspiratory impedance and load compensation: effects of duration of anesthesia. Anesth Analg 1986;65:1–8.

General anesthesia results in increases in respiratory elastance and flow resistance within 10–15 min after induction. Stabilization (compensation) of the respiratory system in the face of this added load is related to the addition of active (contractile) force–length and force–velocity properties to its internal impedance during inspiration. The difference between active (inspiratory) and passive (relaxation–exhalation) values of elastance and resistance can be used as an index of load compensation. We therefore evaluated the effects of duration of anesthesia on respiratory impedance and stabilization by comparing active elastance (E′rs) and flow resistance (R′rs) to their corresponding passive values (Ers, Rrs) at the beginning and end of steady-state breathing in ten young, healthy anesthetized adults undergoing orthopedic surgery (anesthesia ~1.5 MAC of a halogenated anesthetic in 60% N_2O–40% O_2). Occlusion pressure ($P_{0.1}$) and components of ventilation also were measured. Duration of anesthesia did not correlate with changes in active or passive mechanics or with control of ventilation. Mean Rrs increased by 76% ($P < 0.025$), probably due to a decline of atropine effect; however, R′rs increased by only 17%, indicating near-maximum stabilization of flow-resistive properties at the end. Passive elastance increased 6%, whereas E′rs increased 3.8%, indicating essentially constant volume-elastic stabilization throughout. Occlusion pressure increased 20% and V_T/T_I 22%, probably due to a decline in effects of sedation and neuromuscular blockade. We conclude that after induction of anesthesia, the reserve available to overcome flow resistance (intrinsic plus equipment) diminishes but is not related to duration of anesthesia. The reserve available to overcome elastic properties remains essentially constant throughout anesthesia.

Key Words: VENTILATION—pulmonary mechanics. LUNG—ventilatory mechanics.

General anesthesia results in increased total respiratory system elastance (*Ers*) and flow resistance (*Rrs*) in normal individuals, usually within 5–10 min after induction (1–13). Most studies have failed to demonstrate significant changes occurring beyond the first 15 min of anesthesia in resistance to airflow (9,10,13,14), lung elastance (6,7,10), or total respiratory elastance (6,9,13). Most investigators have computed only passive respiratory mechanics, which can be defined as the impedance of the respiratory system due to the volume-elastic impedance (elastance) and flow-resistive impedance (flow resistance) offered by the mechanical properties of the airways, the lung, and the chest wall when the respiratory muscles are relaxed (11). McIlroy et al. (15) made use of this property to measure the elastic (*Ers*) and flow-resistive (*Rrs*) properties in conscious humans. Later Bergman et al. (4,5) and most recently Behrakis et al. (11,12) used the same approach to measure *Rrs* in anesthetized, paralyzed subjects by analysis of flow–volume curves obtained during relaxed expiration.

In contrast to when the respiratory muscles are relaxed, during active inspiration, the force–velocity and force–length properties of the inspiratory muscles add to the internal respiratory impedance: the force–velocity properties add to the flow-resistive impedance and the force–length properties to the volume-elastic impedance (16–18). In addition, to the extent that active breathing may involve distortion of the chest wall from its passive (relaxed) configuration, this also should result in increased active elastance of the respiratory system (18,19). In these studies, the overall impedance of the respiratory system during active breathing could be approximated by a constant elastance (*E′rs*) and a constant resistance (*R′rs*), which henceforth are referred to as active values. Values of *E′rs* and *R′rs* have been determined in anesthetized

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Table 1. Physical Characteristics, Premedication, Anesthetic Agents, and Time Elapsed Between Studies in Ten Subjects

Subject number	Sex	Age (yr)	Height (m)	Weight (kg)	Vital Capacity (L)	Anesthetic (60% N_2O–40% O_2; 7.5 MAC)	Other agents	Interval between studies (hr)
1	M	27	1.68	76.4	4.50	Enflurane	—	0.58
2	M	29	1.70	66.8	4.84	Isoflurane	Fentanyl	0.83
3	M	21	1.52	58.0	4.93	Halothane	—	1.15
4	M	22	1.75	63.2	4.50	Isoflurane	Fentanyl	1.58
5	M	30	1.75	75.0	4.60	Enflurane	—	2.00
6	F	38	1.63	60.9	3.20	Enflurane	—	2.00
7	M	19	1.77	65.9	5.00	Isoflurane	—	2.00
8	F	20	1.51	44.8	3.13	Enflurane	—	2.33
9	F	42	1.63	56.2	3.20	Isoflurane	Fentanyl	4.50
10	M	29	1.73	54.6	4.72	Isoflurane	Fentanyl	5.00
Mean		27.7	1.67	62.2	4.26			2.20
SD		7.7	0.09	9.5	0.77			1.46

cats by Siafakas et al. (16) and Zin et al. (17), and more recently in anesthetized humans by Behrakis et al. (18). Active inspiration is analyzed on the basis of the following equation of motion:

$$-P^{\circ}_{tr} = R'rs \cdot \dot{V} + E'rs \cdot V \qquad (1)$$

where P°_{tr} is tracheal pressure during an inspiratory effort with the airways occluded at functional residual capacity (FRC), and $\dot{V}$ and V are, respectively, the instantaneous flow and volume changes during a control breath immediately preceding the occluded effort (18).

There has been no systematic study of the temporal changes in active respiratory volume-elastic and flow-resistive properties during the course of anesthesia. Because anesthesia results in a decrease in lung volume and increases in total respiratory elastance and resistance within minutes after induction, we wished to determine whether there was a time-dependent change in passive and corresponding active respiratory elastance and resistance after induction. Comparisons between passive and active impedance values would also provide a temporal assessment of respiratory load compensation during anesthesia. In addition, we evaluated control of ventilation by measuring central inspiratory drive from the airway occlusion pressure and derived the effective impedance of the respiratory system from the mean inspiratory flow.

Materials and Methods

Ten patients (7 males, 3 females, aged 19–42) free of cardiorespiratory disease and undergoing general anesthesia for orthopedic reconstructive procedures were studied. Their physical characteristics are summarized in Table 1. After approval by our institutional research ethics committee, informed consent was obtained from all subjects.

Flow ($\dot{V}$) was recorded with a heated Fleisch No. 1 pneumotachograph connected to a breathing circuit and a Validyne MP 45-1 differential pressure transducer. Volume (V) was obtained by integration of the flow signal (Gould Brush integrator). Tracheal pressure (P_{tr}) was measured through a side port mounted at the distal end of the breathing apparatus using another Validyne MP 45-1 pressure transducer. Inspired oxygen concentrations were measured with an Instrumental Laboratories IL-402 oxymeter. All signals were amplified and recorded on a four-channel Gould Brush 2400 recorder. A three-way valve was used to occlude the airway opening or to breathe through three different external linear resistances (ΔR_1, ΔR_2, and ΔR_3) that amounted to 4.7, 13.6, and 53.7 cm $H_2O \cdot L^{-1} \cdot sec$, respectively. These were connected to the inspiratory line and consisted of cigar-shaped porous silica or porcelain chemical filters. All were linear with flows up to 2 $L \cdot sec^{-1}$. The pressure–flow characteristics of the four endotracheal tubes used in the study (7.5, 8.0, 8.5, and 9.0 mm inner diameter) plus pneumotachograph, valve, and connectors (henceforth referred to as equipment) were curvilinear and were defined by Rohrer's equation ($P = K_1\dot{V} + K_2\dot{V}^2$) (11). The flow-resistance constants K_1 (laminar) and K_2 (turbulence) of each tube plus equipment were obtained by dividing both sides of Rohrer's equation by $\dot{V}$ to derive a linear function, $P/\dot{V} = K_1 + K_2\dot{V}$. K_1 and K_2 were then computed by means of regression analysis on experimental values of $P/\dot{V}$ vs $\dot{V}$. K_1 and K_2 for the four endotracheal tubes are given in Table 2. We obtained all resistance values using a gas mixture of 60% N_2O–40% O_2, the same as that used during general anesthesia.

Table 2. Values of K_1 and K_2 of Four Endotracheal Tubes (Including Pneumotachograph and Connectors)

Tube number	K_1 (cm $H_2O \cdot L^{-1} \cdot sec$)	K_2 (cm $H_2O \cdot L^{-2} \cdot sec^2$)
7.5	3.36	7.65
8.0	2.74	6.20
8.5	2.11	5.30
9.0	2.00	3.54

Values pertain to 60% nitrous oxide and 40% oxygen.

Procedure

The patients were premedicated with intramuscular atropine (0.4 mg), hydroxyzine (1 mg/kg), and meperidine (1 mg/kg) or fentanyl (0.05–0.10 mg). Induction was accomplished with thiamylal, alone (6–10 mg/kg) or in combination with fentanyl (0.15 mg). Succinylcholine (1.5 mg/kg) or pancuronium (2 mg) was administered to facilitate intubation. Anesthesia was maintained at a constant minimal alveolar concentration (MAC) of approximately 1.5 with isoflurane, enflurane, or halothane in 60% N_2O–40% O_2, through cuffed endotracheal tubes (7.5, 8.0, 8.5, or 9.0 mm inner diameter). Once respiratory muscle paralysis had worn off (demonstrated by onset of spontaneous respirations), the patient was allowed to breathe until a stable ventilatory pattern was achieved (10–15 min after induction) (20). Every 8–10 breaths the three-way valve was occluded at end-inspiration just long enough to attain a plateau of P_{tr}. This was repeated 5–10 times. This maneuver was followed by a series of two or three end-expiratory occlusions every 8–10 breaths, with each occlusion maintained for one breath. An example illustrating the procedure is shown in Figure 1. During spontaneous breathing, each subject exhibited an end-expiratory pause, i.e., a period of zero flow toward the end of expiration, indicating that the end-expiratory volume was probably the elastic equilibrium point of the respiratory system. This was further supported by the fact that when in the same subjects the airways were occluded at end-expiration, P_{tr} returned to zero (atmospheric pressure) during the occluded expiration. To validate this procedure, linear flow resistances were added at end-expiratory volume in all subjects and maintained for one breath.

All measurements were performed twice. In seven patients, the first set of measurements were made prior to surgery and the second immediately after surgery but before anesthesia was allowed to wear off. In three patients, both sets of measurements were made after induction of anesthesia but prior to the start of surgery. The interval between the two sets of measurements ranged between 0.58 and 5.0 hr (mean ± SD, 2.20 ± 1.46 hr).

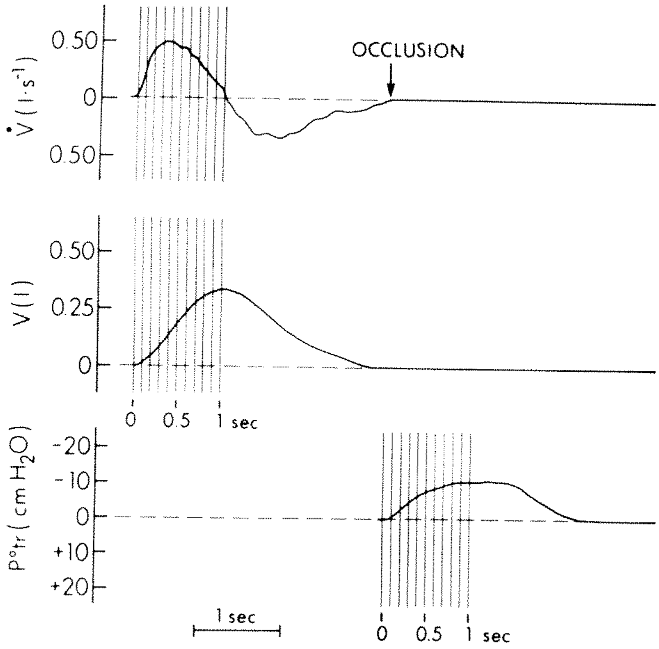

Figure 1. Tracings of flow ($\dot{V}$), volume (V), and tracheal occlusion pressure (P°_{tr}) in a spontaneously breathing anesthetized subject. Occlusion of the airway was performed at end-expiration, as indicated by the arrow, and maintained an entire respiratory cycle. During this period, the patient made an inspiratory effort against the occluded valve as indicated by the negative P°_{tr}, which was measured at 0.1-sec intervals after onset of occluded inspiration. $\dot{V}$ and V were measured similarly. Data plotted according to Equation (2).

Passive hyperinflations ("sighs") were limited to less than one every half hour and averaged approximately twice the tidal volume (0.7–0.8 L). No measurements were made within 5 min of any of these sighs. No patients had any postoperative respiratory complications.

Data Analysis

Active mechanics. $E'rs$ and $R'rs$ were computed by the method of Behrakis et al. (18). The decrease in resistive pressure due to the endotracheal tube and equipment (P_{eq}) was subtracted from the driving pressure, $-P^{\circ}_{tr}$, in Equation (1) and both sides of the equation were divided by $\dot{V}$:

$$(-P^{\circ}_{tr} - K_1\dot{V} - K_2\dot{V}^2)/\dot{V} = R'rs + E'rs\ V/\dot{V} \quad (2)$$

where $(K_1\dot{V} + K_2\dot{V}^2)$ represents the pressure drop due to the equipment. Equation (2) is a linear function of the type $y = a + bx$ where $E'rs$ is the slope and $R'rs$ is the intercept on the y-axis. To construct this linear relationship, P°_{tr}, $\dot{V}$, and V were measured at 0.1-sec

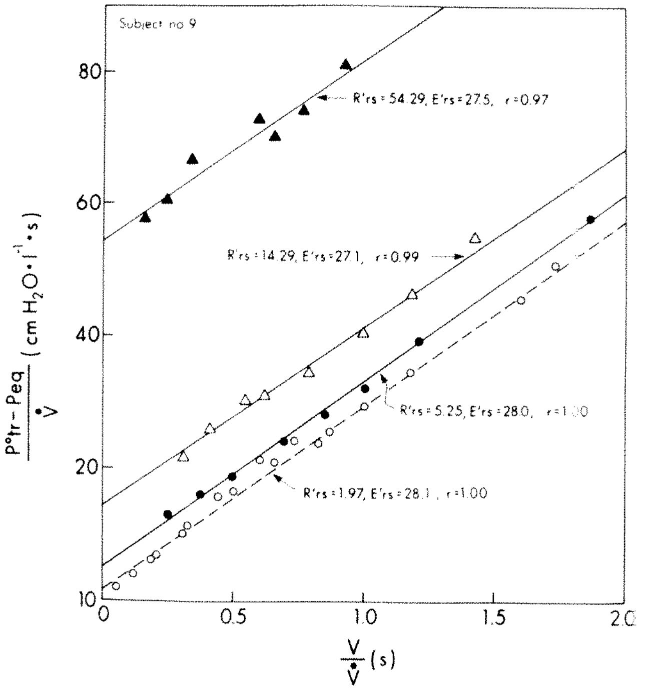

Figure 2. Relationships between $(P^\circ_{tr} - P_{eq})/\dot V$ and $V/\dot V$ in patient number 9 at the end of her study. Broken line and open circles represent unloaded relationship computed for mean of two values of *R'rs* and *E'rs*. Closed circles, open triangles, and closed triangles correspond, respectively, to inspiration loaded with linear resistances of 4.79, 13.68, and 53.7 cm H_2O·sec. Solid lines are regression lines corresponding to data points applied to Equation (3).

intervals after the onset of inspiration. Values of P°_{tr} were obtained during the occluded inspiratory effort; V and $\dot V$ were obtained from the immediately preceding unloaded inspiration. Onset of inspiration was judged as the beginning of inspiratory flow, a negative deflection of P°_{tr}, or both. For each patient, *E'rs* and *R'rs* were computed from the mean of two or three sets of occluded breaths preceding unoccluded breaths.

When one of the linear flow resistances, ΔR, is added to the inspiratory limb of the apparatus, Equation (2) becomes

$$(-P^\circ_{tr} - P_{eq})/\dot V = R'rs + \Delta R + E'rs\ V/\dot V \quad (3)$$

where P_{eq} corresponds to $(K_1\dot V + K_2\dot V^2)$ in Equation (2), and the sum of *R'rs* and ΔR is the intercept of the plot on the *y*-axis. Each loaded breath was compared to the mean of two or three control (occluded-preceding unoccluded) breaths analyzed in every patient.

In all subjects, Equation (2) was found to be linear, proving that this approach is applicable in anesthetized humans (Fig. 2). It also implies that *R'rs* and *E'rs* were constant within the range of volumes (up to 0.5 L) and flows (up to 0.6 L·sec^{-1}) used. After the addition of linear resistances, the intercepts of the relationships in all patients increased by virtually the same amount as ΔR, whereas the slope (*E'rs*) did not change significantly, further validating this approach.

The analysis according to Equation (2) involves two assumptions. The first is that the intensity (rate of rise) of inspiratory neural drive is the same during the occluded and preceding unoccluded inspiration (17,18). Although there is good evidence that in deeply anesthetized animals this is the case for the diaphragm (16), Corda et al. (21) demonstrated that in pentobarbital-anesthetized cats the neural drive to the inspiratory intercostal muscles increased during the first occluded breath at FRC. However, our patients received halogenated inhalational anesthetic agents, of which at least halothane has been shown to preferentially depress the intercostal muscle activity with sparing of diaphragmatic function (22). Accordingly, the assumption of unchanged intensity of inspiratory drive during occlusion in our subjects seems to be reasonably valid. This is also supported by the addition of linear resistive loads (ΔR), during which the increase in intercept (Equation (3)) was always very close to ΔR (Fig. 2). The second assumption is that Equation (2) implies that *E'rs* and *R'rs* are constant during inspiration. A constancy of *R'rs* (and by implication *E'rs*) has been demonstrated in anesthetized cats (23).

Passive mechanics. We also analyzed the passive elastance (*Ers*) and passive resistance (*Rrs*) of the total respiratory system in all patients, using the method of Behrakis et al. (11). The airway was occluded at end-inspiration, and tracheal pressure (P_{tr}) was measured when the patients relaxed their respiratory muscles long enough for P_{tr} to plateau (1–2 sec). The value for *Ers* was obtained by dividing the P_{tr} plateau by the tidal volume. The airway was then opened and the patient allowed to exhale to end-expiratory volume. Analysis of the ensuing relaxed expiratory V–$\dot V$ relationship led to computation of *Rrs* (11). The value for *Rrs* (not including the upper airway) was obtained by subtracting the flow resistance of the equipment and endotracheal tube. Measurements of *Ers* and *Rrs* were repeated 5–10 times and were reproducible.

During measurement of both active and passive respiratory mechanics, potential problems associated with flow-related kinetic energy losses at the junction of the endotracheal tube and trachea were resolved according to the method of Behrakis et al. (11). The passive and active time constants of the respiratory system, τrs and $\tau' rs$, respectively, were obtained as the ratios *Rrs*/*Ers* and *R'rs*/*E'rs*, respectively (17).

Table 3. Active and Passive Elastances, Resistances, and Time Constants at Start and End of Study

	Active						Passive					
Subject number	*E'rs* (cm $H_2O \cdot L^{-1}$)		*R'rs* (cm $H_2O \cdot L^{-1} \cdot sec$)		$\tau'rs$ (sec)		*Ers* (cm $H_2O \cdot L^{-1}$)		*Rrs* (cm $H_2O \cdot L^{-1} \cdot sec$)		τrs (sec)	
	Start	End	Start	End	Start	End	Start	End	Start	End	Start	End
1	33.2	35.3	4.04	4.03	0.122	0.114	29.8	30.1	0.86	4.72	0.029	0.157
2	28.0	24.8	5.25	5.24	0.188	0.212	22.2	21.3	4.09	4.82	0.185	0.226
3	31.1	28.0	1.47	2.54	0.047	0.091	22.0	20.4	1.69	2.37	0.077	0.116
4	30.2	37.9	1.47	5.48	0.049	0.145	21.8	23.4	1.12	4.90	0.051	0.210
5	21.8	20.8	3.97	3.45	0.183	0.166	17.9	18.9	1.24	2.06	0.069	0.109
6	28.2	35.7	5.34	4.87	0.189	0.137	26.3	29.9	2.21	3.55	0.084	0.119
7	30.1	32.5	1.88	6.14	0.062	0.189	19.1	25.3	2.11	5.00	0.110	0.198
8	31.5	30.2	1.45	2.60	0.046	0.086	19.1	22.4	0.58	0.69	0.030	0.031
9	28.0	28.1	6.30	1.97	0.225	0.070	21.0	19.9	2.66	1.88	0.127	0.095
10	25.5	25.9	1.93	2.52	0.076	0.097	21.2	22.7	1.46	1.68	0.069	0.074
Mean	28.8	29.9	3.31	3.88	0.119	0.131	22.0	23.4	1.80	3.17	0.083	0.134
SD	3.3	5.4	1.89	1.48	0.071	0.047	3.6	3.9	1.03	1.62	0.047	0.063
P	NS		NS		NS		NS		< 0.025		< 0.025	

Abbreviations: NS, not significant; *E'rs*, active elastance; *Ers*, passive elastance; *R'rs*, active resistance; *Rrs*, passive resistance; $\tau'rs$, time constant of active respiratory system; τrs, time constant of passive respiratory system.

Significance comparison of corresponding active and passive values: *E'rs* and *Ers*, $P < 0.001$; *R'rs* and *Rrs*, $P < 0.02$ at the start, $P < 0.05$ at the end; $\tau'rs$ and τrs, NS. *P* values for *Ers* and *E'rs* were the same at both the start and end of the study.

Control of ventilation. Inspiratory time (TI) and total breathing cycle (TT) were obtained from the flow signal. Occlusion pressure ($P_{0.1}$) was expressed as the inspiratory pressure obtained 0.1 sec after the onset of inspiratory occlusions (24). It was obtained from the same occluded inspiratory breath used to compute *E'rs*. The "effective impedance" was expressed as the ratio of $P_{0.1}$/(VT/TI) (25). All measurements refer to the average of 2–3 breaths. The coefficient of variation for all parameters of control of ventilation was approximately 15% in all patients.

Statistical analysis. The distribution of the paired differences between corresponding passive and active components of respiratory mechanics, and between corresponding values of mechanics and control of ventilation at the beginning and end of anesthesia (Tables 3 and 4), were inspected for normality using the Shapiro and Wilk's *W*-statistic. The null hypothesis of normality could not be rejected ($P < 0.05$) in any instance. Therefore, significances of differences between pairs of data were computed according to Student's *t*-test, using a significance of $P < 0.05$.

Results

Figure 2 shows a plot of $(-P^{\circ}_{tr} - P_{eq})/\dot{V}$ vs $V/\dot{V}$ obtained in a subject under unloaded conditions and four corresponding loaded inspirations. The linear relationships in all instances showed correlation coefficients (*r*) greater than 0.99. The lines are parallel with the difference between the intercept of the unloaded inspiration and each of the intercepts of the loaded inspirations representing an amount close to the added ΔR. In all ten patients, similar straight relationships with *r* ranging from 0.95 to 1.0 were obtained at both the start and end of anesthesia. Table 3 lists the active values of elastance, resistance, and respiratory time constants obtained under unloaded conditions, together with their corresponding passive values in the 10 patients at the start and end of the study. Values for *Ers*, *E'rs*, *R'rs*, and $\tau'rs$ demonstrated small but nonsignificant increases by the end of the study. However, *Rrs* and τrs increased significantly by 76 and 61%, respectively ($P < 0.025$).

Our values of *R'rs* were, on the average, 83.9% higher ($P < 0.02$) than the corresponding passive values in the beginning of the study and only 22.4% higher ($P < 0.05$) at the end. However on the average, *E'rs* exceeded *Ers* by 30.9% ($P < 0.001$) in the beginning, and by 27.8% ($P < 0.001$) at the end of the study. There was no relationship between individual durations of anesthesia and changes in passive and active respiratory impedance.

Table 4 lists values for control of ventilation. There was no significant change in frequency (*f*), inspiratory time (TI), minute ventilation ($\dot{V}$E), or the "effective" inspiratory timing (TI/TT). On the other hand, VT and VT/TI increased 18.0% ($P < 0.05$) and 22.4% ($P < 0.005$), respectively, by the end of the study. The value of $P_{0.1}$ increased 20.2%, but this was not significant. Because VT/TI increased about as much as $P_{0.1}$, the

Table 4. Ventilatory Parameters and Airway Occlusion Pressure ($P_{0.1}$) in Ten Anesthetized Normal Patients

Subject number	$\dot{V}_E$ (L·min^{-1})		f (breaths·min^{-1})		V_T (L)		T_I (sec)		V_T/T_I (L·sec^{-1})		T_I/T_T		$P_{0.1}$ (cm H_2O)		$P_{0.1}/(V_T/T_I)$ (cm H_2O·L^{-1}·sec)	
	Start	End	Start	End	Start	End	Start	End	Start	End	Start	End	Start	End	Start	End
1	6.17	6.96	21.0	18.5	0.294	0.376	1.18	1.43	0.249	0.263	0.41	0.44	1.83	1.28	7.35	4.87
2	4.07	5.57	16.4	17.5	0.248	0.318	1.70	1.60	0.146	0.199	0.46	0.47	0.95	1.70	6.51	8.54
3	5.59	7.15	22.0	18.0	0.254	0.397	1.05	1.10	0.242	0.361	0.39	0.33	1.13	0.95	4.71	2.64
4	8.56	6.96	19.5	15.0	0.439	0.464	1.15	1.00	0.382	0.464	0.37	0.25	2.90	3.70	7.63	8.04
5	4.25	5.22	15.0	12.1	0.283	0.431	1.45	1.75	0.195	0.246	0.36	0.35	0.50	0.38	2.50	1.52
6	5.57	4.68	15.5	13.8	0.359	0.339	1.60	1.45	0.244	0.234	0.41	0.33	0.81	0.85	3.32	3.63
7	4.65	7.81	13.0	16.0	0.358	0.488	1.55	1.40	0.231	0.349	0.34	0.37	0.70	1.30	3.03	3.73
8	4.25	5.46	14.5	16.0	0.293	0.341	1.43	1.47	0.205	0.232	0.35	0.39	0.84	0.62	4.10	2.67
9	6.90	7.14	15.0	20.0	0.460	0.357	1.55	1.15	0.297	0.310	0.39	0.38	1.18	1.71	3.97	5.52
10	4.43	6.80	15.0	19.2	0.295	0.354	1.70	1.45	0.174	0.244	0.43	0.46	0.60	1.20	3.45	4.92
Mean	5.44	6.38	16.7	16.6	0.328	0.387	1.44	1.38	0.237	0.290	0.39	0.38	1.14	1.37	4.66	4.61
SD	1.45	1.04	3.0	2.5	0.074	0.057	0.23	0.23	0.066	0.080	0.04	0.07	0.72	0.92	1.85	2.29
P	NS		NS		< 0.05		NS		< 0.01		NS		NS		NS	

Abbreviations: NS, not significant; $\dot{V}_E$, minute ventilation; f, respiratory frequency; V_T, tidal volume; T_I, inspiratory duration; V_T/V_I, mean inspiratory flow; T_I/T_T, effective inspiratory timing; $P_{0.1}$, occlusion pressure at 0.1 sec; $P_{0.1}/(V_T/T_I)$, effective impedance.

"effective impedance," $P_{0.1}/(V_T/T_I)$, did not change, consistent with the lack of significant change in *E'rs* and *R'rs*. Again, there was no correlation between length of anesthesia and changes in $P_{0.1}$, V_T, $\dot{V}_E$, and V_T/T_I.

Discussion

As shown in Table 3, the values for *Ers* in our anesthetized subjects averaged 22.0 and 23.4 cm H_2O·L^{-1} at the start and end of the study period, respectively (change not significant). They were higher than corresponding values for unanesthetized normal subjects (~10 cm H_2O·L^{-1}) and in agreement with previous reports on humans anesthetized with halothane (11,18) and isoflurane (9). Values of *E'rs* were, on the average, about 30% higher than *Ers* ($P < 0.001$). A similar difference (34%) has been found previously in halothane-anesthetized individuals by Behrakis et al. (18), whose values of *Ers* and *E'rs* were similar to ours (mean ± SD, 23.2 ± 3.7 and 31.2 ± 5.2 cm H_2O·L^{-1}, respectively).

Our values of *Rrs* and *R'rs* were higher overall (1.80 and 3.31 cm H_2O·L^{-1}·sec, respectively, at the beginning and 3.17 and 3.88 cm H_2O·L^{-1}·sec, respectively, at the end of the study) than values reported by Behrakis et al. (mean values for *Rrs* and *R'rs* 1.8 and 2.1 cm H_2O·L^{-1}·sec, respectively) (18), the differences being statistically significant for the end-study *Rrs* and both sets of *R'rs* ($P < 0.001$). This discrepancy may reflect the fact that four of our patients received fentanyl, which is known to cause bronchoconstriction (26,27).

Factors that may have contributed to the increase in flow resistance by the end of the study include a decrease in FRC resulting from a cephalad displacement of the diaphragm. This would result in an increase in *Rrs* and *R'rs*. However, it would also result in increases in *Ers* and *E'rs*, which did not occur. In addition, a change in FRC should result in a change in static lung recoil [$P_{st}(L)$]. In our study, $P_{st}(L)$ measured by the esophageal balloon technique of Baydur et al. (28), averaged 7.9 cm H_2O at the beginning and 7.5 cm H_2O at the end (difference not significant). Given the relative constancy of *Ers*, *E'rs*, and $P_{st}(L)$, it is unlikely that the increased flow resistance resulted from a decrease in FRC. This is in agreement with other investigators who showed that FRC did not decrease progressively after an initial decline that occurred immediately after induction (29–32). The effect of atropine was probably wearing off and may also have contributed to the increase in *Rrs* and *R'rs*. Don and Robson (33) noted that the atropine-induced decrease in flow resistance is most likely due to a genuine change in bronchomotor tone rather than a change in end-expiratory volume. As the bronchodilating effect of atropine declines, both *Rrs* and *R'rs* will increase. We favor this mechanism.

Although intrinsic *Rrs* increased by 76%, *R'rs* increased by only 17%, indicating a smaller "reserve" available for stabilization of flow–velocity properties during the latter stages of anesthesia. In contrast, active elastance increased by only 3.8%, closely approximating the 6% in its corresponding passive value. This implies that stabilization of volume-elastic properties did not change throughout anesthesia. The effects of the changes in passive and active flow-resistive and volume-elastic impedance are also reflected in the passive and active time constants of the respiratory system (τrs and $\tau' rs$, respectively) (Table 3). The value of $\tau' rs$ is larger than τrs at the beginning of the study, reflecting the relatively larger difference between *Rrs* and *R'rs* than between *Ers* and *E'rs*. As *Rrs* increased proportionately more than *R'rs*, the difference between τrs and $\tau' rs$ became unapparent (because (*E'rs*–*Ers*) remained virtually constant). These findings suggest that, at least in early anesthesia, in relation to the passive respiratory system, the pressure losses during active breathing due to force–velocity properties of the system were greater than pressure losses due to force–length properties. As flow resistance increased with waning vagolytic action, intrinsic stabilization approached maximum, diminishing the difference between passive and active resistance (i.e., the reserve available for load compensation). These results, at least at the beginning of anesthesia, are in contrast to those of Behrakis et al. (18), who found that as a result of a greater increase in elastance (34%) than intrinsic resistance (17%) during active breathing, the active intrinsic time constant was somewhat shorter (0.067 sec) than corresponding passive values (0.079 sec). Again, these differences can be accounted for by the use of fentanyl in four of the subjects, resulting in greater active flow resistance values (3.3 cm $H_2O \cdot L^{-1} \cdot sec$) than those reported by Behrakis et al. (2.1 cm $H_2O \cdot L^{-1} \cdot sec$) (18). In this connection, because of the highly curvilinear flow resistance offered by the endotracheal tubes, the overall (tubes included) behavior of either the passive or active respiratory system cannot be characterized by single time constants (18), as was the case in cats studied by Siafakas et al. (16) and Zin et al. (17), in which the equipment resistance was linear within the experimental range of flows.

Accurate measurement of *Rrs* and *R'rs* in intubated subjects requires an assessment of the contribution of the endotracheal tube (*Req*) to the total resistance while under anesthesia. However, separate in vitro values of *Req* alone have sometimes been reported to be greater than the combined resistance of *Rrs* (or *R'rs*) + *Req* in vivo. This results from kinetic energy losses at the junction between the tube and the trachea (34,35). Methods used to circumvent the need to estimate this kinetic energy dissipation have included measurement of airway pressure with the use of a small catheter placed some distance beyond the tip of the endotracheal tube (36). This method may give variable results, depending on the position of the catheter tip with respect to gas flow. Use of a tight-fitting tracheal cannula with airway pressure measured close to the trachea-cannula junction is another method used. Although losses due to lumen widening are small, this method is invasive and can be used only in tracheotomized patients (34). Another method involves separate measurement of the resistance due to the pressure drop across a combined equipment-endotracheal tube-artificial trachea system (11,12). A smooth-bore tube simulating the trachea is mounted on the distal end of the endotracheal tube, extending about 10 cm beyond its tip. We used this method, to which we applied Rohrer's relationship in computing the constants K_1 and K_2 for our equipment-trachea model in vitro and subtracting them from the K_1 and K_2 values derived from the intubated patients. In every case the K_2 of the intubated patient was virtually the same as or slightly exceeded the K_2 of the in vitro tube model. These findings validated the use of the tube–trachea model for determining the contribution of the endotracheal tube to the total airway resistance.

We found no relationship between central drive and active elastance or flow resistive properties. The correlations between $P_{0.1}$ and *E'rs* were poor both at the start and end of the study period ($r = 0.50$ in both situations). Similarly, the correlations between $P_{0.1}$ and *R'rs* were even worse ($r = 0.17$ at the start and $r = 0.41$ at the end of the study). These findings suggest that the interindividual variabilities in central drive and active impedance were too great to define a cause and effect relationship between them.

By relating $P_{0.1}$ to VT/TI, we can assess whether changes in mechanics of the respiratory system contributed to the increase in VT/TI (24). An increase in the effective impedance, $P_{0.1}$/(VT/VI), would have suggested that respiratory drive increased in response to an increased internal impedance. Yet in our study, although both mean $P_{0.1}$ and VT/TI increased, mean $P_{0.1}$/(VT/TI) did not change significantly, indicating that the increase in drive was probably not due to a change in respiratory elastance and resistance, but to a decline in the effects of sedative and neuromuscular blocking drugs. In this connection, there was no relationship between the different anesthetic agents used and changes in active and passive values of respiratory impedance or in changes of ventilation. Thus it appears that halogenated volatile anesthetics have similar quantitative and temporal effects on respiratory mechanics and load compensation.

In summary, we have shown that in young adults undergoing premedicated general anesthesia, passive and active values of respiratory elastance do not increase significantly beyond the first 10 min of anesthesia, up to at least 2 hr. In contrast, there was a small increase in flow resistance (although it remained at the upper range of normal for anesthetized adults). This small change was not time-dependent and was attributed to an increase in bronchomotor tone as atropine action declined. We demonstrated a small increase in respiratory drive that can be explained on the basis of declining sedation and neuromuscular blockade. The increase in drive was not related to changes in passive or active impedance. Comparisons of passive and active respiratory mechanics under anesthesia in older patients and in patients with pulmonary and chest wall disorders should further enhance understanding of respiratory load compensation.

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Ventilatory and Circulatory Responses to Carbon Dioxide and High Level Sympathectomy Induced by Epidural Blockade in Awake Humans

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DOHI S, TAKESHIMA R, NAITO H. Ventilatory and circulatory responses to carbon dioxide and high level sympathectomy induced by epidural blockade in awake humans. Anesth Analg 1986;65:9–14.

In order to examine the effects of cervico-thoracic epidural block with 1.5% lidocaine on ventilatory and circulatory responses to carbon dioxide, the authors studied the CO_2–ventilatory response curves and the changes in heart rate (HR) and blood pressure (AP) to rebreathing of exhaled gas before and after the block in healthy volunteers. Neither resting ventilation nor ventilatory response to CO_2 was affected by the epidural block (mean analgesic level extended from C4 to T7); the slope of the CO_2–ventilatory response curve averaged 2.38 ± 0.81 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$ (mean ± SD) before and 2.32 ± 0.82 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$ after the block. Resting HR and AP decreased significantly ($P < 0.01$) after the block, but responses in HR and AP to CO_2 rebreathing were not significantly changed by the block. Plasma concentrations of norepinephrine and epinephrine were similar before and after the block both with and without CO_2 rebreathing. These results indicate that high levels of sympathetic denervation induced by epidural block do not impair circulatory and ventilatory responses to carbon dioxide in awake, healthy humans.

Key Words: VENTILATION—carbon dioxide response. CARBON DIOXIDE—hypercarbia. ANESTHETIC TECHNIQUES, EPIDURAL.

High levels of epidural anesthesia do not appear to be associated with clinically significant circulatory (1–5) or ventilatory (2,6,7) changes unless concentrations of local anesthetics used are great enough to produce paralysis of intercostal and phrenic nerves (8–10). On the other hand, high levels of epidural anesthesia are associated with sympathetic blockade that may affect responses of circulatory and ventilatory systems to stimuli, such as respiratory acidosis, that normally produce significant increases in sympathetic activity (11–13). The present study was designed to determine how high levels of sympathetic denervation during epidural anesthesia modify cardiovascular and respiratory responses to acute respiratory acidosis.

Methods

Seven healthy male medical students, aged 23 or 24 yr, volunteered to participate in this study, which was approved by our Institutional Review Committees. Subjects refrained from caffeine or alcohol-containing beverages for 12 hr and took nothing by mouth for 6 hr before they were studied.

In each subject an intravenous catheter was inserted for infusion of lactated Ringer's solution (4–5 $ml \cdot kg^{-1} \cdot hr^{-1}$), and a radial arterial catheter was inserted for direct measurements of arterial blood pressure (AP) and for sampling of arterial blood. Electrocardiogram, heart rates (HR) calculated on a beat-to-beat basis (1321, Tachometer, Sanei Co., Tokyo) and AP were recorded throughout the study.

Each subject was placed in the supine, horizontal position and told to listen to symphonic music through headphones while breathing in a quiet, relaxed fashion through a face mask (dead space volume, 40 ml), which connected to a hot-wire spirometer of a constant temperature type (Respiromonitor, RM-200, Minato Med. Science, Osaka) (14) and a CO_2 analyzer (Datex, Finland). These were calibrated using a 1000-ml rolling calibrating syringe and standard gas mixtures, respectively. Tidal volume (V_T), respiratory rates (RR), expired minute volume ($\dot{V}_E$), and end-tidal concentration of carbon dioxide (ET_{CO_2}) were recorded digitally every 30 sec by a recorder (Epson, MP 80). All volumes were converted to BTPS.

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Table 1. Data (mean ± 1 SD) during Resting Control Conditions and during CO_2 Rebreathing before and after Cervical Epidural Block

	Before the block		After the block	
	Resting	At the end of CO_2 rebreathing	Resting	At the end of CO_2 rebreathing
HR (beats/min)	66 ± 8	79 ± 8[a]	59 ± 7[b]	72 ± 7[a]
AP (mm Hg)	123 ± 9	144 ± 15[a]	118 ± 10[b]	139 ± 10[a]
RR (min^{-1})	11 ± 2	16 ± 3	13 ± 2	14 ± 2
$\dot{V}_T$ (ml)	552 ± 90	1761 ± 372[a]	458 ± 89	1960 ± 435[a]
$\dot{V}_E$ ($L \cdot min^{-1}$)	5.9 ± 0.6	27.4 ± 3.5[a]	6.0 ± 0.7	27.6 ± 6.1[a]
Pa_{O_2} (mm Hg)	94.6 ± 3.7	339.3 ± 51.8[a]	90.7 ± 3.8	329.6 ± 47.8[a]
Pa_{CO_2} (mm Hg)	41.1 ± 1.6	55.4 ± 3.7[a]	43.0 ± 2.1	57.0 ± 5.1[a]
pHa	7.423 ± 0.011	7.331 ± 0.031[a]	7.414 ± 0.014	7.314 ± 0.026[a]
Base excess ($mEq \cdot L^{-1}$)	2.6 ± 1.0	2.1 ± 1.1	3.1 ± 0.7	1.3 ± 1.6
Epinephrine ($ng \cdot ml^{-1}$)	0.038 ± 0.002	0.043 ± 0.004	0.031 ± 0.004	0.035 ± 0.001
Norepinephrine ($ng \cdot ml^{-1}$)	0.097 ± 0.031	0.098 ± 0.027	0.115 ± 0.037	0.111 ± 0.045

[a] $P < 0.01$ vs resting; [b] $P < 0.01$ vs before the block.

After 5 min of quiet breathing, the responses to endogenous CO_2 were assessed by the method of Read (15). A dead-space circuit (7-L bag and corrugated tube filled with oxygen, CO_2, and air) was connected to the face mask. Oxygen was added to the system to meet metabolic requirements and to maintain a constant volume in the rebreathing apparatus. After a progressive increase in ET_{CO_2}, the test was terminated at an ET_{CO_2} of 7.0–7.5%, which was usually achieved within 6 min. Two arterial blood samples were taken for blood gas analyses and for measurements of plasma concentrations of norepinephrine and epinephrine; one during a quiet breathing and the other at the time just before termination of rebreathing.

After the control measurements, each subject received cervical epidural block in the lateral decubitus position. After intradermal and subcutaneous injection of 1–2 ml of 1% lidocaine at the C7–T1 intervertebral space, a 17-gauge Tuohy needle was inserted into the epidural space using the loss-of-resistance technique. After the identification of the epidural space, 10 ml of 1.5% lidocaine without epinephrine was injected through the needle. Each subject then was placed in the supine position. The level of analgesia in each subject was measured using the pinprick method 20 min after the injection. The ventilatory and circulatory responses to endogenous carbon dioxide were then measured again in the same way as before the epidural block. Two arterial blood samples were also obtained 20 min after the epidural injection and just before termination of the rebreathing test.

CO_2–ventilatory response curves were constructed for each subject before and after the block. The slope of each curve is the difference between ventilation ($\dot{V}_E$) at low (43–46 mm Hg) and high (55–57 mm Hg) end-tidal CO_2 tension divided by the difference in measured CO_2 tension. Plasma catecholamine concentrations were determined by high-pressure liquid chromatography using the system based on the trihydroxyindole reaction (limits of assay sensitivity > 10 pg/ml).

Statistical significance of changes of the slope, HR, and AP before and after the block was determined by Student's t-test. A value of $P < 0.05$ was taken as indicating significance. All values are expressed as mean ± 1 SD.

Results

The levels of analgesia were C3.9 ± 0.4 to T6.9 ± 0.9. Though the time of onset of analgesia and the levels of analgesia were similar in all subjects, there were minor variations among subjects in the extent of motor blockade in the upper extremities. No subject complained of respiratory difficulty aside from nasal congestions associated with bilateral positive Horner's syndrome seen in all subjects after the block. There were no statistically significant changes in arterial blood gas tension or plasma concentrations of norepinephrine and epinephrine after the block (Table 1).

Ventilatory Response

The cervical epidural block caused no significant change in resting ventilation (Table 1) or in the CO_2–ventilatory response curves in any subject (Table 2). Expiratory minute volume ($\dot{V}_E$) increased similarly with increases in end-tidal P_{CO_2} (mm Hg) both before and after the block (Fig. 1). The mean values of calculated slope of

Table 2. Subject Characteristics and the Slopes ($L \cdot min^{-1} \cdot mm\ Hg^{-1}$) of the CO_2–Ventilatory Response before and after the Cervical Epidural Block

	Subject				Slope ($L \cdot min^{-1} \cdot mm\ Hg^{-1}$)	
	Age (yr)	Body weight (kg)	Height (cm)	Analgesic levels	Before block	After block
	23	54	170	C_4–T_7	2.68	1.84
	23	62	173	C_4–T_7	1.81	1.59
	23	70	179	C_4–T_8	2.82	3.58
	24	67	178	C_3–T_7	1.63	2.67
	23	60	177	C_4–T_7	1.27	1.19
	23	66	173	C_4–T_7	2.96	2.81
	23	65	172	C_4–T_5	3.45	2.59
Mean ± 1 SD	23 ± 0.4	63 ± 5	175 ± 3	C3.9 ± 0.4–T6.9 ± 0.9	2.38 ± 0.81	2.32 ± 0.82

the CO_2–response curves before the block was 2.38 ± 0.81 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$ (mean ± 1 SD); after the establishment of epidural block, the slope did not change (2.32 ± 0.82 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$). After the block, the increases in RR (10%) and in V_T (266%) after CO_2 rebreathing were different from the 40% increases in RR and 190% increase in V_T before the block. Two subjects who showed decrease in RR associated with increases of V_T during the rebreathing before epidural block also showed a similar pattern of respiratory response to CO_2 after the block.

Circulatory Response

The cervical epidural block caused a slight but statistically significant decrease in resting HR (9.5 ± 3.8% below control levels) and AP (8.7 ± 8.3%). The cervical epidural block did not, however, cause any significant change in the magnitude of the increases in HR and AP in response to CO_2 rebreathing (Table 1, Fig. 2). The percent increases in HR and AP from control levels during the rebreathing were 19.9 ± 3.7 and 17.4 ± 7.1 before the block, and 23.4 ± 5.4, 17.9 ± 3.8 after the block.

Discussion

The results of the present investigation show that subjects with lower cervical and upper thoracic sympathetic denervation are able to preserve circulatory and ventilatory responses to accumulation of endogenous carbon dioxide, at least within the limitations of the present study. The extent of sensory blockade from C4 to T7 clearly indicates that sympathetic innervation of the heart, lung, and peripheral vasculature of upper extremities, thorax, and neck were blocked at the epidural levels. Bilateral Horner's syndrome also indicates that sympathetic innervation of peripheral chemoreceptors was also blocked. Because we used a high concentration of a potent local anesthetic, 1.5% lidocaine, to ensure complete preganglionic sympathetic denervation in the lower cervical and upper thoracic segments, respiratory muscles might have been partly blocked (8,9), though we could not detect this. In addition, pharmacologically active plasma concentrations of lidocaine might have been achieved in our subjects after epidural block using 1.5% lidocaine; using 2% lidocaine without epinephrine for cervical epidural block results in plasma concentrations of lidocaine greater than 2.5 μg/ml 7–30 min after the epidural injection (16). This plasma level of lidocaine might affect both circulatory (17,18) and ventilatory function (19,20) to some extent, but the effect must have been relatively minor in view of the statistically insignificant differences in both circulatory and ventilatory responses to CO_2 challenges before and after the block in the present study.

It is well known that carbon dioxide is the most important chemical stimulus for ventilation. Because cervical preganglionic sympathetic stimulation increases the frequency of sinus nerve chemosensory discharges (11–13), probably due to blood flow changes (21), we considered that the elimination of this by epidural blockade might depress the CO_2–ventilatory responses. However, we could not demonstrate this expectation. This may be because ventilatory and cardiovascular responses to peripheral chemoreceptor stimulation produced by increases in arterial P_{CO_2} are less important than the effect of increases in P_{CO_2} on central chemoreceptors (22); the former attributes less than 20% of the ventilatory response to CO_2 in a normal subject. Also, and perhaps more likely, lidocaine, both by bolus injection and by infusion, may produce significant changes in CO_2–ventilatory response curves in awake humans. Gross et al. (20), for example, found that lidocaine infusion (serum concentration of 3.5 ± 0.2 μg/ml) increased the slope of CO_2–response curves,

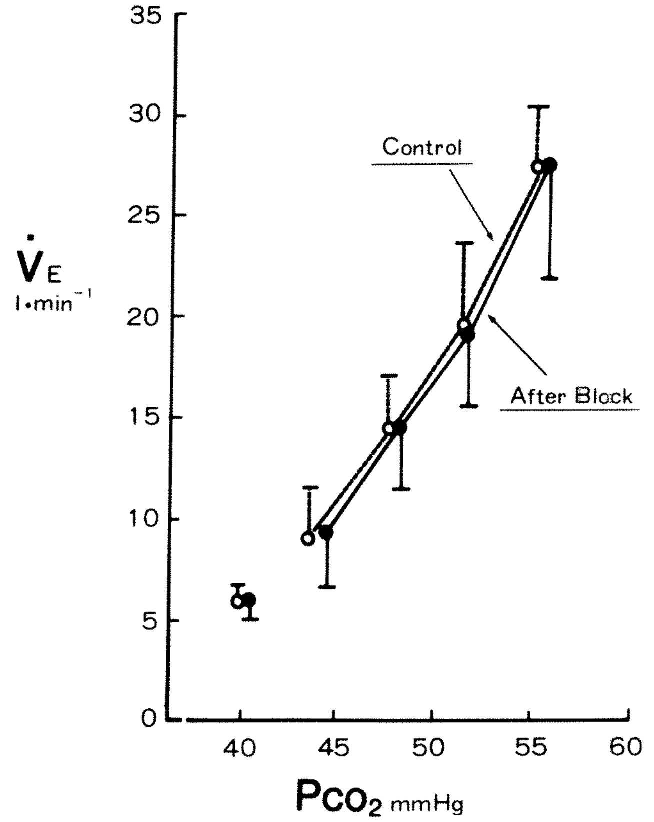

Figure 1. Minute ventilation ($\dot{V}_E$) end-tidal CO_2 (P_{CO_2}) curves before (control) and after cervical epidural block. Values are means ± 1 SD.

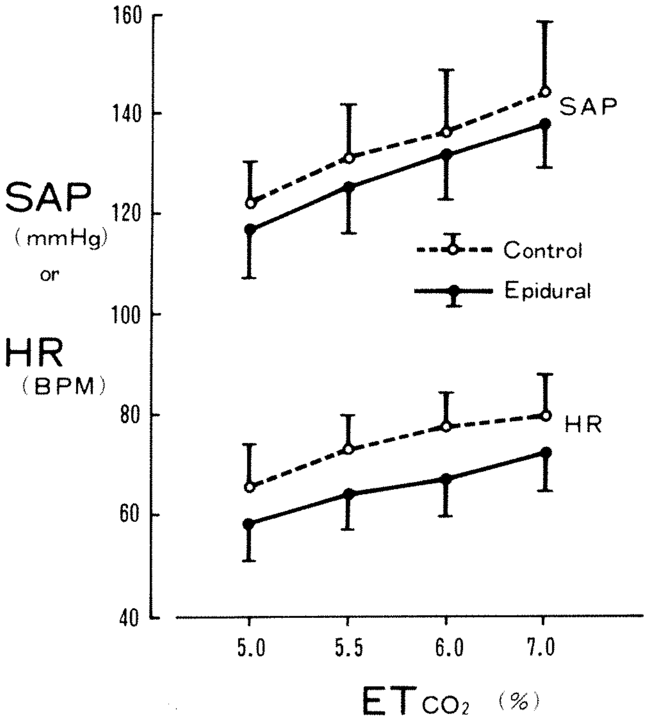

Figure 2. Changes in systolic arterial pressure (SAP) and heart rate (HR) as a function of end-tidal CO_2 (ET_{CO_2}) before (control) and after cervical epidural block.

suggesting that studies of ventilatory control in subjects receiving conduction anesthetics must take into account the direct effect of absorbed local anesthetics on ventilatory control. Thus we cannot completely exclude the possibility that the pharmacological action of plasma lidocaine achieved after the block might hinder or counteract the neurologic effects on CO_2–ventilatory responses to CO_2 in the present study.

Cross et al. (22) have reported that the aerosol anesthesia of the airways with 5% bupivacaine significantly enhanced the ventilatory response to CO_2 ($\dot{V}_E/CO_2$) in conscious humans, principally by increasing respiratory frequency, though intravenous administration of bupivacaine (1–1.3 μg of plasma concentration) did not affect $\dot{V}_E/CO_2$. Because respiratory frequency responses to changes in pulmonary CO_2 are likely to result from changes in pulmonary stretch receptors located in the peripheral regions of the lungs (23), it is possible that a local anesthetic may sensitize the receptor responses to CO_2 or that blockade of the receptors in the larger airways by bupivacaine aerosols may contribute to the enhancement of the CO_2–ventilatory responses observed by Cross et al. (22). In the present study, we observed increases in V_T rather than increases in respiratory frequency during CO_2 stimulation after the epidural block. How the sympathetic denervation of lungs at epidural level affects local pulmonary receptor activity and modulates such receptor function to CO_2 deserves further study.

Systemic hypercapnia induces cardiovascular changes due to significant increases in sympathetic activity in both humans and animals (13,24,25,26). An increase in CO_2 tension has two opposite actions on the normally innervated cardiovascular system (25,27): one, a direct effect of the carbon dioxide on the peripheral vessels resulting in vasodilation; the other, mediated through the response of the vasomotor center to an increase in CO_2 tension, producing peripheral vasoconstriction. After sympathetic denervation, the circulatory responses to CO_2 are different (28,29) in that carbon dioxide accumulation then results in further vasodilation of sympathetically denervated vessels with a consequent further decrease in arterial blood pressure (29). Galindo (30) observed that total epidural blockade produced further decreases in AP when CO_2 was added to inspired gas than did the blockade itself in anesthetized, paralyzed dogs. More recently it was also found that cervical epidural blockade partially suppresses ketamine-induced cardiovascular effects (31). This latter effect apparently is due to denervation of sympathetic cardiac efferents that normally mediate changes in central sympathetic tone to the heart. However, in the present study of awake humans the magnitudes of the changes in HR and AP responding to CO_2 were not statistically different before and after the block, although the resting HR and AP decreased significantly (about 9%) after the block. The reason for this is unclear. Because there is experimental evidence that systemic hypercapnia excites sympathetic preganglionic neurons and thus increases AP and HP even in the spinal-cord transected animals (32,33), the absence of suppressive effects in the present results seem possible. A recent experimental study in the spinal rat with denervation of peripheral chemoreceptors demonstrates that CO_2 induces a neurogenic hypertensive response even in the absence of respiratory activity (32). In addition, even in patients with cervical epidural block, a potent stimulus such as laryngoscopy and tracheal intubation elicits circulatory responses (4). Therefore, it seems likely that the high-level sympathectomy by epidural block preserves heart rate and blood pressure responses to potent stimuli. Subjects with high thoracic epidural block also have normal cardiovascular responses to exercise (3).

The hemodynamic effects of the epidural block may also be caused by interaction with adrenomedullary function. Plasma concentrations of norepinephrine and epinephrine were little changed after the epidural block, and the rebreathing before or after the block caused no increase in these plasma levels. Because the blockade did not involve preganglionic neurons of the lower six thoracic segments, which are responsible for the sympathetically mediated release of catecholamines from the adrenal medulla, it is not unexpected that the cervical block did not decrease resting plasma concentrations of circulating catecholamines. This differs from the observation that thoracic epidural analgesia produced inconsistent and insignificant changes in levels of circulating catecholamines in pentobarbital-anesthetized dogs (34). On the other hand, during acute hypercapnia, circulating levels of catecholamines increase. Recently, using the same method we used for measuring plasma catecholamine concentration, Rose et al. (35) reported that acute hypercapnia (Pa_{CO_2} 53 ± 1 mm Hg; pH 7.19 ± 0.02) increased circulating norepinephrine levels along with increases in MAP, cardiac output, and heart rate in awake dogs, whereas circulating epinephrine remained unchanged during acute hypercapnia. The release of norepinephrine from postganglionic nerve terminals has been reported to be inhibited by local anesthetics (36), and sympathetic innervation of the adrenal medulla might have been partially blocked in the present study. Therefore, our results were expected.

Good preservation of circulatory and ventilatory responses to CO_2 during high level sympathectomy certainly could provide us with reassurance in some clinical situations, such as management of postoperative pain, as well as chronic pain. Our finding may also support a use of cervical epidural block for patients with ischemic heart disease because high level segmental sympathetic denervation, even with possible pharmacologic side effects, has been found to have beneficial effects in such patients (37,38). However, because it is evident that the cervical and thoracic sympathetic ganglia that affect circulation and ventilation through baroreceptors, chemoreceptors, or both, are very complex (32,39,40), further studies are necessary before the physiologic significance of our observations can be understood in terms of the clinical management of patients with ischemic heart disease.

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Midazolam as an Intravenous Induction Agent in the Elderly:
A Clinical and Pharmacokinetic Study

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KANTO J, AALTONEN L, HIMBERG JJ, HOVI-VIANDER M. Midazolam as an intravenous induction agent in the elderly: a clinical and pharmacokinetic study. Anesth Analg 1986;65:15–20.

Midazolam, the first benzodiazepine derivative with water-soluble salts, was studied as an induction agent in general anesthesia for the elderly. In group 1 (n = 14), 5 or 10 mg oral diazepam was used as premedication, but in group 2 (n = 9), both oral (10 mg dixyrazin as a night-time sedative) and intramuscular (0.01 mg/kg atropine + 1 mg/kg meperidine) premedicants were used. Serum concentrations of benzodiazepines were determined using both gas–liquid chromatographic (unchanged midazolam) and radioreceptor assays (binding equivalents of benzodiazepines plus their active metabolites). In general, midazolam, 0.15 mg/kg, intravenously resulted in smooth induction of anesthesia, although the time required for induction was rather long and a sudden but transient decrease in blood pressure was found in a significant number of patients. The course of anesthesia was otherwise satisfactory. A marked amnesic effect was observed, especially when diazepam was used as premedication. The pharmacokinetic parameters based on gas–liquid chromatographic measurements were quite comparable with those in young, healthy persons published earlier. In both groups, the binding equivalents measured with radioreceptor assay (reflecting total benzodiazepine activity) were higher than the levels of unchanged midazolam determined with gas–liquid chromatography. The relatively low dose of 0.15 mg/kg of midazolam needed for anesthetic induction in the elderly indicates not pharmacokinetic, but pharmacodynamic, alterations in older patients. We conclude that midazolam is a new intravenous induction agent for use in the elderly, but careful titration of the dosage according to the response of the patient is required. Diazepam premedication prior to midazolam causes a marked anterograde amnesic effect.

Key Words: HYPNOTICS, BENZODIAZEPINES—midazolam. INDUCTION, ANESTHESIA—midazolam.

The steadily growing number of geriatric patients seen in everyday anesthetic practice is nowadays clearly recognized (1–3). The pharmacodynamic (4–8) and pharmacokinetic (8–12) changes that take place with age result in many benzodiazepines having more pronounced effects on the central nervous system. The greater sensitivity of the elderly to psychoactive drugs is a general phenomenon (8) and, pharmacokinetically, changes in both the distribution and elimination of a specific agent are suspected to lead to an exaggerated clinical response (12).

In our earlier studies with intravenous flunitrazepam as a sedative or for induction of anesthesia, we observed clinical responses that were greater in the elderly than in younger patients without, however, differences in pharmacokinetics of flunitrazepam as a function of age (3,6,7). In addition to the increase in the central sedative–hypnotic effect, sudden and unexpected decreases in blood pressure were found in some poor-risk patients, especially at the beginning of anesthesia induced with intravenous flunitrazepam (3). In the present study we evaluate the use of midazolam, the first water-soluble 1,4-benzodiazepine derivative, as an induction agent in elderly patients. Its pharmacokinetics were calculated in order to evaluate any alterations in kinetic parameters as a function of age. The main advantages of this new agent over older benzodiazepine derivatives are its short and more predictable duration of action and a low frequency of venous irritation (13,14). The short drug action without residual effects makes midazolam in the elderly particularly worth studying.

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Patients and Methods

Twenty-three elderly patients were included in this study. In group 1 (8 males and 6 females; mean age 73.4 yr, range 67–79; mean weight 69.1 kg, range 60–87; mean height 165.4 cm, range 147–176; ASA class III, n = 11 and ASA class IV, n = 3) patients received 5 mg oral diazepam if they weighed less than 60 kg or 10 mg if they weighed more than 60 kg as a night-time sedative the evening before surgery and also as a premedication given about 2 hr before operation. In group 2 (4 males and 5 females; mean age 72.3 yr, range 65–78; mean weight 61.3 kg, range 51–78; mean height 165.1 cm, range 155–188; ASA class III, n = 7 and ASA class IV, n = 2) patients received 10 mg oral dixyrazin as a night-time sedative the evening before surgery. Their premedication consisted of intramuscular atropine (0.01 mg/kg) and meperidine (1 mg/kg) given about 1 hr before the operation. In both groups, most of the patients were on multidrug therapy (mostly different analgesic and cardiovascular drugs), and only those being treated with benzodiazepines were excluded from the study. In terms of diseases and drug therapies the two groups were comparable. The patients were scheduled for various general surgical procedures. Anesthesia lasted 194.1 min (range 97–350 min) in group 1 and 175.6 min (range 65–240 min) in group 2.

Two minutes before induction of anesthesia with midazolam, 0.15 mg/kg intravenously (Dormicum, Roche), droperidol (dehydrobenzperidol), 0.03 mg/kg, and fentanyl, 1 μg/kg, were given intravenously to prevent unwanted cardiovascular effects and to hasten induction (15). The times to spontaneous closing of the eyes and to disappearance of the palpebral reflex were recorded. Tracheal intubation was facilitated with intravenous succinylcholine, 1.2–1.4 mg/kg, followed by intravenous pancuronium (group 1: 0.09–0.23 mg/kg, mean 0.15 mg/kg; group 2: 0.09–0.18 mg/kg, mean 0.13 mg/kg). N_2O plus O_2 (60/40) was given throughout anesthesia, and fentanyl was administered when necessary (group 1: 2.6–10.5 μg/kg, mean 7.6 μg/kg; group 2: 3.1–8.2 μg/kg, mean 5.2 μg/kg). The anticurarizing agents used were atropine, 1.0–1.4 mg, and neostigmine, 2.5 mg intravenously. Heart rate and systolic and diastolic blood pressures were monitored at 5-min intervals (using a sphygmomanometer) before and during anesthesia, as well as in the recovery room.

Blood samples for measurement of serum benzodiazepine levels were drawn from the antecubital vein just before the administration of midazolam and then 3, 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 3, 6, and 8 hr after midazolam administration. The drug concentrations were determined using both radioreceptor assay (RRA, binding equivalents of benzodiazepines plus their active metabolites; group 1: n = 12, group 2: n = 7) (16) and gas-liquid chromatography (GLC, unchanged midazolam; group 1: n = 10, group 2: n = 7) (17). The objective in measuring drug levels with RRA was to indicate benzodiazepine activity caused by diazepam premedication before the induction of anesthesia in group 1 and the total benzodiazepine activity in both groups after midazolam induction (i.e., total binding activity caused by diazepam and midazolam plus their active metabolites). On the other hand, GLC measures only the levels of unmetabolized midazolam (18). Thus RRA measurements better quantitate the total response to all benzodiazepines and their active metabolites, while GLC is used for pharmacokinetic calculations. The reproducibility of RRA was good (intraassay variation < 5%, interassay variation < 5% at the concentration level of 16.3 ng/ml midazolam, n = 10). The GLC method was specific and sensitive enough for pharmacokinetic studies (midazolam recovery 74%; day-to-day and within-day coefficient of variation ranged from 7 to 9%; lower limit of detection, 2 ng/ml).

The degree of postoperative sedation was determined by the anesthesiologist (MHV) 5 min, 1 hr, and 2 hr after the end of anesthesia (asleep, very sedated, moderately sedated, alert). The first day after surgery the same anesthesiologist asked the patient if he or she remembered coming to the operating theatre, intravenous infusion starting, waking up from anesthesia, the time spent in the recovery room, returning to the ward, or events during the evening on the day of operation. The pharmacokinetic parameters of midazolam (GLC) were calculated using a two-compartment open model as in our earlier studies (18–20).

Results

The fairly low dose of 0.15 mg/kg of intravenous midazolam resulted in smooth induction of anesthesia. In group 1, the eyes were spontaneously closed in 59.3 sec (range 20–120) and in group 2 in 45.0 sec (range 40–65). The palpebral reflex disappeared in 106.1 sec (range 60–180) and in 72.8 sec (range 50–110). Cardiovascular stability during and after anesthesia was generally good, but 3–15 min after the beginning of midazolam induction, a clinically significant but transient decrease (>30%) in systolic blood pressure occurred in 5 of 14 patients in group 1 and in 4 of 9 patients in group 2. The lowest values, 70–90 mm Hg, were found in three patients in group 1 and in two patients in group 2. A single 3–4 mg intravenous dose of etilefrin, a sympathomimetic agent, was sufficient to rectify the situation.

In one patient (group 1) suffering from cardiac insufficiency and rheumatoid arthritis (on digoxin, methylprednisolone, and indomethacin therapy) bronchospasm occurred 10 min after midazolam injection for which 200 mg of aminophylline was slowly injected intravenously and 0.25 mg of terbutaline given subcutaneously with satisfactory resolution of the bronchospasm. Postoperatively, the patient stated that she had been awake and experienced nightmares during the anesthesia. Earlier she had been anesthetized nine times with no problems, and she was very dissatisfied with the present anesthesia. According to the anesthesiologist, the patient was in deep sleep and there were no signs that anesthesia was too light.

None of the patients was still asleep 5 min after the end of anesthesia, but most patients were very (group 1: 7/14; group 2: 7/9) or moderately sedated (group 1: 7/14; group 2: 2/9) at this time. In the recovery room 12/14 patients in group 1 were moderately sedated or alert both 1 and 2 hr after the end of anesthesia. The corresponding numbers of patients in group 2 were 6/9 and 7/9, respectively. Two patients in both groups were very sedated during the 2-hr period in the recovery room, and one of them (group 2) needed artificial ventilation for 4 hr because of hypoventilation and dyspnea.

The day after anesthesia, 2/14 patients in group 1 did not remember coming to the operating theatre and 6/14 could not recollect the starting of intravenous infusions. In group 2 the respective figures were 0/9 and 2/9. In group 1, 13/14 patients did not remember waking up from anesthesia, 11/14 had no recollection of the time spent in the recovery room, 9/14 could not remember returning to the ward, and 2/14 could not remember anything of the day of the operation. In group 2 the respective findings were 4/9, 2/9, 1/9, and 0/9.

Figure 1 shows the serum drug levels in groups 1 and 2 measured with GLC (unmetabolized midazolam) or with RRA (binding equivalents of all active benzodiazepines). In both groups, RRA measured higher levels than GLC, and after diazepam premedication in group 1 a mean serum level of 66.1 ng/ml was present just before induction of anesthesia (Fig. 1). The pharmacokinetic parameters of midazolam were calculated from GLC determinations in groups 1 and 2. Three earlier studies in younger subjects carried out by our group are presented for comparison (Table 1). The patients of Sjövall et al. (20) (age 54.8 ± 18.4 (SD) yr) received midazolam before spinal analgesia and those of Kanto et al. (19) (mean age 29 yr, range 20–32) during cesarean section in order to deepen anesthesia once the baby was delivered. In the study of Aaltonen et al. (18) the patients in group 1 were undergoing hysterectomy under epidural analgesia (mean age 42 yr, range 35–60) and those in group 2 were undergoing hand surgery under brachial plexus blockade (mean age 38 yr, range 21–70). In general, no important pharmacokinetic differences were seen between younger (18,19) and elderly patients. The volume of distribution of β-phase was somewhat higher in the elderly, but it was clearly more increased during pregnancy (20).

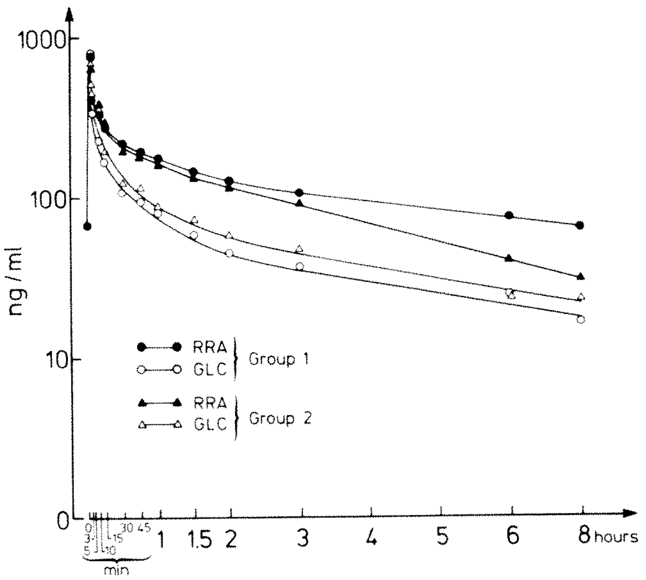

Figure 1. Mean serum concentrations of benzodiazepines in groups 1 and 2 measured by RRA and by GLC. Patients in group 1 were premedicated with oral diazepam and those in group 2 with oral dixyrazin and intramuscular atropine plus meperidine. Anesthesia was induced with intravenous midazolam, 0.15 mg/kg, in both groups. GLC determined only the concentrations of unmetabolized midazolam in both groups, but RRA determined levels representing the activity of both orally administered diazepam, intravenously injected midazolam plus their active metabolites in group 1, and those of midazolam plus its active metabolites in group 2.

Discussion

Our results show that the first water-soluble benzodiazepine derivative, midazolam, is a suitable induction agent for elderly patients. Generally, it resulted in smooth induction of anesthesia, but the time to induction was longer than is usual with thiopental. The condition of the patients was satisfactory during the perioperative and postoperative periods except for a transient decrease in systolic blood pressure at the beginning of anesthesia in a significant number of our

Table 1. Pharmacokinetic Parameters of Midazolam (mean ± SD) in Elderly Surgical Patients Based on GLC Determination of the Drug in Serum

n	Dose	$t_{1/2\alpha}$ (hr)	$V_{d\alpha}$ (L/kg)	$t_{1/2\beta}$ (hr)	$V_{d\beta}$ (L/kg)	Cl_{tot} (ml·min^{-1}·kg^{-1})	Reference
10	0.15 mg/kg IV	0.08 ± 0.04	0.24 ± 0.13	5.6 ± 4.8	1.68 ± 0.46	5.61 ± 3.12	Present study group 1
7	0.15 mg/kg IV	0.09 ± 0.03	0.22 ± 0.09	5.9 ± 5.2	1.59 ± 0.56	4.71 ± 2.73	group 2
6	0.075 mg/kg IV	5.7 ± 4.6 (min)	0.41 ± 0.17	1.4 ± 0.4	1.21 ± 0.95	630 ± 352 (ml/min)	Sjövall et al. 1983 (20)
8	0.075 mg/kg IV	10.1 ± 3.4 (min)	0.39 ± 0.14	103.5 ± 22.3 (min)	2.97 ± 1.31	11.50 ± 3.90	Kanto et al. 1983 (19)
6	0.075 mg/kg IV	0.10 ± 0.04	0.19 ± 0.08	1.5 ± 0.5	0.91 ± 0.42	6.52 ± 2.55	Aaltonen et al. 1984 (18) group 1
6	0.075 mg/kg IV	0.12 ± 0.04	0.18 ± 0.05	2.0 ± 0.8	0.95 ± 0.52	5.02 ± 0.98	group 2

The results of three of the authors' earlier studies are also included for comparison.

Abbreviations: $t_{1/2\alpha}$, distribution phase half-life; $t_{1/2\beta}$, elimination phase half-life; $V_{d\alpha}$, volume of distribution of α-phase; $V_{d\beta}$, volume of distribution of β-phase; Cl_{tot}, total serum clearance.

patients. In our earlier study with flunitrazepam as an intravenous induction agent in the elderly, we observed the same phenomenon (3). This may be due to the α-blocking property of the previously administered intravenous droperidol or, more likely, to a peripheral vasodilatator effect, possibly due to histamine release caused by benzodiazepines (21), or to cardiac output depression. Midazolam produces light sedation requiring powerful premedication (15), and hence the third possibility is an interaction between our premedication and midazolam. It may be possible to avoid hypotension by giving midazolam in small intravenous increments according to the patient's response. In this study, however, a fixed dose was used because of the pharmacokinetic nature of the study.

In comparison with flunitrazepam (3), the main difference was the slight residual sedation caused by intravenous midazolam. Despite this, there was a high incidence of postoperative amnesia in the present patients, especially after oral diazepam premedication. The high combined affinity of all active benzodiazepines in serum determined by radioreceptor assay may provide an explanation for the greater amnesic effect in patients receiving benzodiazepine premedication.

When an amnesic effect is undesirable, oral dixyrazin in the evening and intramuscular atropine plus meperidine are more suitable than oral diazepam as premedication for the elderly when midazolam is to be used for induction of anesthesia. The amnesic effect of preanesthetic medication may not be desirable in every patient because it is often associated with loss of self-control that may be alarming (22).

Intravenous aminophylline at the very modest dose of 60 mg has been reported to counteract deep diazepam sedation (23–25), apparently by adenosine blockade of GABA-receptors in the CNS (25). In the present study, one patient given intravenous aminophylline, 200 mg, and subcutaneous terbutaline, 0.25 mg, intraoperatively for treatment of bronchospasm claimed to be partially awake during anesthesia and experienced nightmares. With the exception of the new enprofylline (25), methylxanthines probably antagonize benzodiazepine sedation, and they should not be used in benzodiazepine-induced anesthesia.

Generally, the pharmacokinetic parameters of midazolam were comparable in the present study of elderly patients with those of younger, healthier subjects published earlier by us (18–20), indicating pharmacodynamic alterations with advancing age as the explanation for greater response to midazolam. In young healthy patients, at least 0.30 mg/kg of midazolam should be administered intravenously to induce clinical anesthesia (15,26). In the present and in our earlier study (15), the same kind of premedication was used, but in the present study of elderly patients 0.15 mg/kg of midazolam was found to be adequate.

In earlier studies (27–29), the distribution volume of midazolam in the β-phase in the elderly has been shown to be somewhat higher than in younger subjects. A similar phenomenon was found in our studies, also (Table 1), except that pregnancy appears to increase this value clearly more than age does (19). In pregnant patients, however, no increased response to midazolam has been found (19,30) and, hence, the changed distribution volume probably does not explain the more pronounced response of midazolam in the elderly.

Binding equivalents determined by RRA techniques apparently reflect the concentrations of all benzodiazepines used plus their active metabolites, thus reflecting the total therapeutic activity in humans (16,18,30). The serum concentrations in group 2 without benzodiazepine premedication measured by RRA were somewhat higher than those determined by GLC after a single 0.15 mg/kg intravenous injection of midazolam (the difference is the active metabolites of midazolam). In one of these patients, however, traces of benzodiazepine activity (RRA) were found in the control sample taken before midazolam induction. Although patients were questioned, and those admitting to previous benzodiazepine treatment were excluded from this study, the possibility remains that some patients falsely claimed no prior benzodiazepine treatment. In earlier studies (31), the concentration of the main metabolite of midazolam, 1-hydroxymethylmidazolam, in the serum varied from 40 to 100% of that of the parent drug, indicating the clinical importance of this metabolic product. In the present study, the mean area under curve (AUC) value measured by RRA was 18% higher in group 2 without benzodiazepine premedication than that measured with GLC, apparently reflecting the amount of active metabolites of midazolam after intravenous administration in the elderly. Thus these two methods can be used to separate the parent drug from its active metabolites.

The half-life of 1-hydroxymethylmidazolam is approximately 1 hr (31,32), and it would seem that neither this nor any other metabolite extends the duration of action of midazolam (33). The main metabolite is produced in higher concentrations in the first 2–3 hr after a single intravenous injection of midazolam (31), reflecting the greatest difference at these times in the serum levels measured by RRA and GLC in group 2. Nevertheless, this main metabolite should be taken into consideration when comparing the serum levels and clinical effects of midazolam treatment.

In conclusion, midazolam is a new induction agent suitable for use in the elderly when a slow induction time is acceptable in view of the benefits derived: low frequency of venous irritation, production of anterograde amnesia, and short duration of action in comparison with other benzodiazepines. Intermittent drug injection in accordance with the response of the patient also guarantees good cardiovascular and respiratory stability. Because of the pharmacodynamic alterations, a reduced dose should be used in the elderly.

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Is Enflurane Hepatotoxic?

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EGER EI II, SMUCKLER EA, FERRELL LD, GOLDSMITH CH, JOHNSON BH. Is enflurane hepatotoxic? Anesth Analg 1986;65:21–30.

We evaluated 88 cases of hepatic injury that followed, and were attributed to, enflurane anesthesia. In 30 of the cases, data were insufficient to assess the role of enflurane vs other variables as causal factors. In 43 ("unlikely") patients, factors known to produce hepatic injury were clearly present; in the remaining 15 ("possible"), such factors were not evident. No consistent pathologic change was found in liver specimens from either the unlikely or the possible group of cases. A syndrome suggested to be associated with enflurane-induced hepatic injury was present in both groups and did not differ between groups. We conclude that the data do not demonstrate a causal relationship between enflurane anesthesia and subsequent liver injury and that if severe injury is caused by enflurane anesthesia, it is an extremely rare event.

Key Words: ANESTHETICS, VOLATILE–enflurane. LIVER–hepatotoxicity.

The benefits conferred by therapeutic agents are sometimes offset by the injury they cause. Although sensitive biological assays exist to detect such injury, they may be inadequate if the injury produced is very small or rare, or if it affects one species but not another. Thalidomide represents one such example. Another is the anesthetic fluroxene, which is safe in humans but lethal in several nonprimate species (1).

As a result, sometimes the rare injury some drugs produce is identifiable only by anecdotal reports of injury that are related temporally to the administration of the drug in question. The existence of a large number of such reports may suggest a relationship, particularly if the associated findings are consistent (i.e., if a syndrome exists) and unique.

Since the release of the halogenated inhaled anesthetic enflurane in 1972, 10 reports of liver damage after administration of enflurane have been published (2–11). Reviewing these reports and other unpublished data, Lewis et al. (12) concluded that enflurane caused the damage in some but not all of these instances. Patients seemingly injured by enflurane often had signs, symptoms, and histories reminiscent of halothane-induced hepatitis (e.g., chills, fever as a presenting sign, nausea, anorexia, rash, eosinophilia, and previous exposure to a halogenated anesthetic). Furthermore, Lewis et al. suggested that characteristic (but not pathognomonic) changes in liver structure occurred (e.g., "The hepatic lesion associated with enflurane toxicity is characterized primarily by centrilobular necrosis similar to that of halothane- or methoxyflurane-induced injury.") We have examined the material reviewed by these investigators and have come to different conclusions.

Methods

In addition to the published reports of hepatic injury (2–11), several unpublished reports were received by the US Food and Drug Administration (FDA) and by the Armed Forces Institute of Pathology (AFIP). In all instances, one or more of the attending physicians suggested a possible association between enflurane administration and subsequent liver injury.

Our review evaluates reports from the release of enflurane in 1972 to January 1983. After we excluded duplicate material, 88 cases remained. We did not include an additional five patients with liver injury after chemotherapy and enflurane anesthesia (13). For 30 of the 88 cases (34%), the available information was insufficient to permit an evaluation of the cause of injury, and these cases were set aside ("inadequate information" cases). Data for inadequate information

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cases commonly were provided on one-half to one page forms (Drug Experience Report) sent to the FDA. The remaining 58 cases (66%) were divided into 43 cases in which factors known to produce liver injury were clearly present ("unlikely" cases), and 15 cases in which such factors could not be discerned or in which the effect of such factors seemed insufficient to have produced the subsequent injury ("possible" cases). A similar approach was taken by Lewis et al. in their review.

Although both possible and unlikely cases probably were subject to reporter bias, such a bias would apply to both groups. We assumed that liver injury in the possible cases might have resulted from enflurane administration, whereas injury in the unlikely cases probably resulted from other causes. If this assumption is correct, then a comparison of the characteristics of these two groups would reveal whether a syndrome was associated with liver injury in the possible group but not with injury in the unlikely group, and whether histologic abnormalities distinguished the possible group.

We examined each report for demographic data (e.g., age, gender); for factors said to be associated with enflurane-induced hepatitis (e.g., rash, anorexia, eosinophilia); for signs of liver injury (e.g., increased serum transaminase levels, hepatic histologic changes); and for conditions that might injure the liver directly or predispose the liver to injury (e.g., hypoxia, shock, congestive heart failure, alcoholism, exposure to known hepatotoxins, viral hepatitis, peritonitis, and septicemia).

Slides of liver specimens were available for four patients in the possible group and for 12 patients in the unlikely group. Two specimens also were available for two patients in the inadequate information group. After the slides were coded and arranged in random order, they were examined independently and "blindly" by two of us (EAS and LDF). Each liver was given a score from 0 (no injury) to 3 (maximum injury) based on injury to liver cells and, separately, on injury to liver ducts. In addition, slides for each liver were examined for the presence of centrilobular necrosis; the recentness of the injury; the presence of unique changes (e.g., Mallory bodies); involvement of the endothelium; the presence and type of fibrosis (bridging, central, or portal); and the presence and distribution of inflammation. We also examined slides for the existence of a consistent lesion in either the possible or unlikely groups.

The features recorded for the two groups then were compared with a two-tailed Student's t-test, Fisher's exact test, or χ^2 analysis (without application of Yates' correction factor). We accepted a P value of less than 0.05 as significant. To avoid a type II error (i.e., a β error), we did not apply a Bonferroni correction despite the multiple comparisons made (14). Agreement between EAS and LDF in "blinded" evaluations of tissues was analyzed using a κ or uniform weighted κ (15).

Finally, we devised a "syndrome score" from the suggestions made by Lewis et al. (12) and from H. J. Zimmerman (personal communication). Each report was examined for 12 variables:

1. prior anesthesia with a halogenated anesthetic,
2. fever as a presenting sign,
3. chills,
4. nausea,
5. anorexia,
6. rash,
7. eosinophilia,
8. an observation of jaundice by the attending physicians,
9. a total bilirubin level exceeding 2.5 mg/dl,
10. a value for serum glutamic-oxaloacetic transaminase (SGOT) above 370 IU (i.e., more than ten times the upper limit of the normal range),
11. the presence of centrilobular necrosis,
12. death of the patient.

Each positive item was given a score of 1; then the sum of the positive items was divided by the total number of variables for which data were available. A syndrome score was thus derived for each patient. For example, a surviving patient might have had a previous anesthesia with a halogenated anesthetic, fever as a presenting sign, jaundice, a bilirubin level of 6.8 mg/dl, and an SGOT level of 550 IU, but no nausea, anorexia, or eosinophilia; information might not have been available regarding the presence of chills, rash, or centrilobular necrosis. Thus the syndrome score would have been 5/9 or 0.56.

The average scores of the possible and unlikely groups were compared using Student's t-test. No attempt was made to weight individual items (e.g., the occurrences of rash, eosinophilia, or an SGOT value ten times higher than normal were all given one point). Thus the scoring system emphasized liver damage, that is, jaundice, the bilirubin value, the SGOT value, and centrilobular necrosis constitute a third of the score items but clearly are not independent variables.

Results

Ten differences existed between the possible and unlikely groups (Table 1). The patients in the possible

Table 1. Enflurane-Induced Liver Injury: Characteristics of the Possible and Unlikely Groups

	Possible group			Unlikely group				
Variable	*n*	Value or %	SEM	*n*	Value or %	SEM	t or χ^2	*P*
Age (yr)	15	40.9	4.8	43	55.8	2.4	2.79	0.01
Women	15	60%	—	43	37%	—	2.36	NS
Minutes of anesthesia	15	159	28	43	127	13	1.05	NS
Narcotic given during anesthesia	14	86%	—	27	74%	—	0.73	NS
History of allergy	11	64%	—	27	33%	—	2.94	NS
Prior exposure to halogenated anesthetic	13	77%	—	31	48%	—	3.04	NS
Days to onset of symptoms	15	2.7	0.9	42	6.7	1.4	2.50	0.02
Fever as a presenting sign	15	60%	—	41	61%	—	0.00	NS
Peak temperature (°C)	13	38.6	0.2	30	39.3	0.1	2.45	0.02
Jaundice	15	67%	—	42	67%	—	0.00	NS
Eosinophilia	14	29%	—	28	21%	—	0.26	NS
Peak eosinophil count (%)	11	4.2	1.1	22	6.1	2.5	0.73	NS
Rash	11	9%	—	24	13%	—	0.09	NS
Chills	9	44%	—	25	16%	—	2.98	NS
Nausea	10	90%	—	29	55%	—	3.92	0.05[a]
Anorexia	13	100%	—	31	77%	—	3.49	NS[a]
Diarrhea	9	22%	—	28	14%	—	0.32	NS
Encephalopathy	13	15%	—	35	46%	—	3.72	0.04[a]
Renal failure	15	7%	—	40	40%	—	5.68	0.025
Peak SGOT (IU)	15	794	250	39	1643	479	1.57	NS
Log peak SGOT[b]	15	2.74	0.09	39	2.70	0.11	0.27	NS
Patients with SGOT > 370 IU	15	73%	—	39	49%	—	2.66	NS
Peak LDH (IU)	9	628	110	33	1446	355	2.20	0.05
Log peak LDH	9	2.80	0.07	33	2.84	0.09	0.81	NS
Patients with LDH > 1490	9	0%	—	33	30%	—	3.58	NS[a]
Peak SGPT (IU)	12	1032	238	16	1169	413	0.29	NS
Log peak SGPT	12	2.82	0.16	16	2.70	0.15	0.53	NS
Peak alkaline phosphatase	11	260	45	36	332	54	1.02	NS
Log alkaline phosphatase	11	2.32	0.10	36	2.39	0.05	0.61	NS
Peak bilirubin (mg/dL)	13	9.4	2.8	38	11.8	2.1	0.70	NS
Log bilirubin	13	0.73	0.14	38	0.84	0.08	0.69	NS
Patients with bilirubin > 2.5 mg/dl	13	69%	—	38	76%	—	0.26	NS
Obese	13	46%	—	33	61%	—	0,79	NS
Major cavity surgery	15	20%	—	43	65%	—	9.10	0.005
History of hypertension	15	13%	—	35	34%	—	2.29	NS
Postoperative hypotension	13	23%	—	34	41%	—	1.33	NS
Postoperative congestive failure	15	0%	—	32	34%	—	6.73	0.01
Postoperative hypoxia	13	33%	—	34	79%	—	8.57	0.005
Anemia	12	17%	—	32	44%	—	2.77	NS
Low hemoglobin (g/dl)	9	11.5	0.6	28	10.7	0.4	1.19	NS
Transfusion	15	33%	—	39	54%	—	1.83	NS
Number of units	14	1.2	0.9	36	3.4	0.9	1.81	NS
Infection	13	31%	—	36	61%	—	3.53	NS[a]
Centrilobular necrosis	3	33%	—	19	79%	—	2.72	NS
Died	15	13%	—	41	34%	—	2.33	NS

Abbreviations: NS, not significant; SGOT, serum glutamic-oxaloacetic transaminase; LDH, lactic dehydrogenase; SGPT, serum glutamic-pyruvic transaminase.

[a] Fisher's exact test.

[b] Log values are also given because of the skewed nature of the data.

group were younger and displayed symptoms sooner. Nausea occurred more frequently in this group; and encephalopathy, renal failure, congestive heart failure, hypoxia, and surgery involving a major cavity occurred less frequently. Also, values for peak temperature and lactic dehydrogenase (LDH) were lower for the possible group.

No comparison of individual items revealed significant differences between the possible and unlikely groups regarding the variables examined histologi-

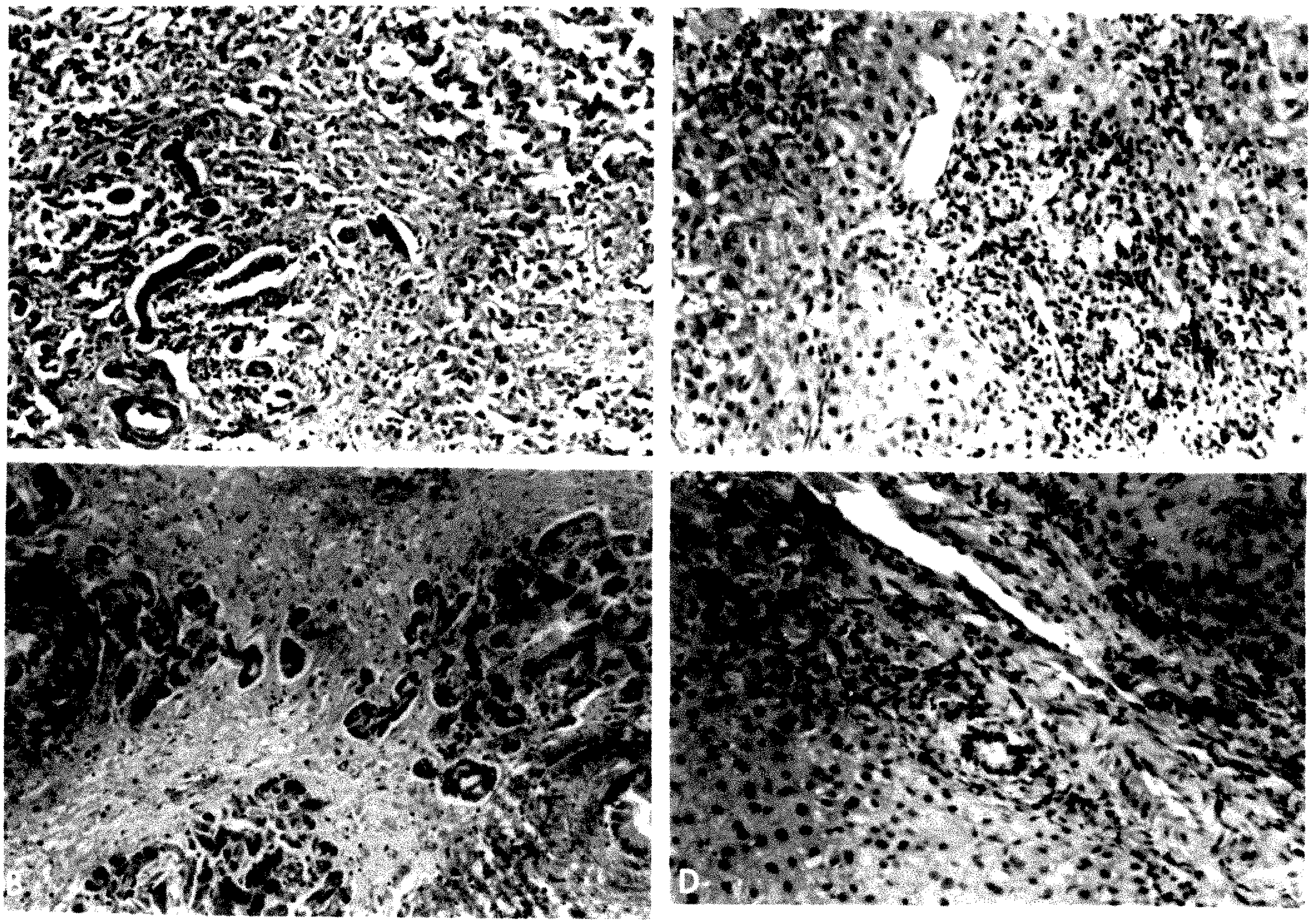

Figure 1. Illustration of the inconsistent appearance of liver injury. Specimens of liver were obtained from four of the probable cases of enflurane-induced hepatitis. (**A**) and (**B**) show tissue obtained at autopsy, whereas (**C**) and (**D**) show tissue obtained by needle biopsies. (**A**) [Lewis et al., (12) FDA Case #6] reveals acute massive necrosis with only rare cells remaining around the portal tract (note artery of portal tract in upper right portion of figure) (× 125). (**B**) [Lewis et al., (12) AFIP Case #4] also shows massive necrosis now replaced by extensive scarring, most prominent in the central venous regions. Fibrosis extends into portal tracts (lower right), and regeneration is suggested by the tubular or "glandular" changes of hepatocytes (× 125). (**C**) [Kline (8)] shows marked mononuclear inflammatory infiltration of portal tracts (center) and parenchyma reminiscent of acute viral hepatitis. Occasional liver cell necrosis without localization to the central venous areas is seen (upper right and left) (× 200). (**D**) [Lewis et al., (12) FDA Case #1] shows a mild portal tract inflammatory infiltrate with neither piecemeal nor significant parenchymal necrosis (× 200). A rare acidophilic body was noted (not shown). These figures illustrate the variable nature of the injury to the liver and the absence of a consistent or characteristic picture of liver injury after enflurane anesthesia in the probable group.

cally, and no trend distinguished one group from the other. (The maximum t value was 0.78 for a comparison of the average score of injury to liver ducts: the average score in the unlikely group was 0.86, whereas that in the possible group was 0.61. The maximum χ^2 value was 0.95 when the two groups were compared regarding percentage of cases showing inflammatory cells: 94% in the possible group was 78% in the unlikely group.) For example, necrosis scores for two of the four livers in the possible group were 1.5 or less, and scores for six of the 12 livers in the unlikely group were 1.5 or less (the mean score for the possible group was 1.5; and for the unlikely group, 1.8). Both groups had diverse manifestations of the degree and type of injury (Fig. 1). Agreement between the evaluations of EAS and LDF was reasonable. For example, for the overall degree of liver injury, the weighted agreement was 0.8, the weighted κ estimate 0.45, and $P = 0.0005$, indicating good agreement. For the classification of centrilobular necrosis, the raw agreement was 0.89, the kappa estimate 0.80, and $P < 0.0001$, indicating excellent agreement.

The syndrome score for the possible group was 0.566 ± 0.025 (mean ± SEM) and was not significantly different from the score of 0.523 ± 0.032 for the unlikely group. Given the variability found for the two groups, the difference that occurred would be significant if each group consisted of about 300 patients. Alternatively, if the sample sizes were unchanged, detection of a significant difference with a power in excess of 0.8 would require a difference of 0.167.

Discussion

The rarity of severe liver damage after anesthesia with modern halogenated anesthetics makes a prospective randomized investigation of their relationship to liver damage economically infeasible. The estimated incidence of less than one in 10,000 for liver necrosis after halothane (16) means that a precise estimate of the incidence might require the collection of at least 30,000 cases. If, as suggested by Lewis et al. (12), the incidence is less with enflurane, then a still larger sample would be needed.

Even so, the determination of such an estimate would not reveal whether these injuries were attributable to enflurane itself or to other perioperative factors. The relative incidence of injury could be defined by a cohort study, that is, by the use of a comparison group (e.g., a group of patients anesthetized with halothane or with nitrous oxide–narcotic). If, however, the injury were very rare (e.g., one per 100,000), the demonstration of a doubling of such an incidence secondary to the use of enflurane could require the collection of data on more than one million patients.

A more feasible approach is represented by the case–control study, which collects data on all patients having unexplained postoperative hepatic dysfunction. These data then are examined for their association with administration of a particular anesthetic (i.e., enflurane vs no enflurane). Case–control studies of 200 cases and 200 controls would allow for detection of the doubling of risk (17,18). After ten years of use of enflurane, only 88 cases had been reported; therefore, an additional ten years might be necessary to acquire the requisite number. Even so, such a study would only demonstrate the hepatotoxicity of enflurane if the incidence of hepatic injury were significantly higher for patients given enflurane. The absence of a difference would not rule out the possibility that enflurane injures the liver: enflurane and the comparison agents might be equally toxic. Indeed, even the finding of a lower incidence in patients anesthetized with enflurane would only indicate that enflurane was less hepatotoxic than the anesthetics with which it was being compared. Furthermore, if enflurane is not a hepatotoxin, it is not possible to prove such an absence of toxicity [e.g., one cannot disprove the existence of dragons (19)].

And so we turn to volunteered reports such as those used in this analysis. Although this method of evaluating toxicity has been touted as being both effective and economical (20), it also has severe limitations. Some of these limitations were discussed in the preceding two paragraphs. In addition, the absence of a control group eliminates any scientific credibility concerning the definition of an association.

Some insights result from our examination of the anecdotal reports of enflurane-induced hepatitis. First, if enflurane causes liver injury, that injury does not consistently result in centrilobular necrosis, as suggested by Lewis et al. (12) (Fig. 1). The absence of a characteristic lesion suggests that either enflurane does not induce injury or that the appearance of the lesion is determined by multiple factors.

Second, a comparison of the characteristics of individuals in the possible and unlikely groups does not reveal differences that suggest enflurane is a hepatotoxin.

Third, the comparison of syndrome scores reveals no significant difference. Presuming that enflurane-induced liver injury in the possible group, whereas injury resulted from other causes in the unlikely group, the absence of a significant difference between the two groups calls into question the existence of the syndrome offered by Lewis et al. This presumption may be incorrect. Perhaps enflurane caused the hepatic injury in both the possible and the unlikely groups. In that case, the relatively high syndrome scores for each group (see the fourth point, below) would support the argument for a hepatotoxic effect of enflurane. However, this line of reasoning requires that we discount the alternative causes of injury to the liver suggested for the unlikely group. For example, we would have to discount the documented invasion of the liver by herpes virus that occurred in one of the unlikely patients (see Table 2 for other examples). We and Lewis et al. (investigators with clearly opposing biases) agree that the hepatic injury in the majority of the unlikely patients was attributable to causes other than enflurane.

Fourth, these data suggest that a reporter bias exists because of our present perception of halothane-induced hepatitis. Note that the patients in the unlikely group had a syndrome score of 0.522 (i.e., the average individual in this group had 52.2% of the syndrome characteristics). Our clinical impression is that the average patient undergoing anesthesia and surgery does not have this high a syndrome score.

We believe that these cases were reported because

Table 2. Rationale for Our Exclusion of 11 Cases Believed by Lewis et al. (12) to Represent Enflurane-Induced Liver Injury[a]

Reference	Rationale for exclusion
Ona et al. (7)	Abnormal serum transaminase level prior to anesthesia; evidence of hemolysis and sepsis; evidence of alcoholism.
White et al. (10)	Congestive heart failure after cardiopulmonary bypass (pump time, 136 min) for triple-valve disease in which six units of whole blood, six units of plasma, and four units of platelets were given.
AFIP Case #1	Peritonitis, septicemia (positive blood cultures), adult respiratory distress syndrome, and shock.
AFIP Case #2	Sepsis, hypoxemia, hypotension.
AFIP Case #3	Jaundice and increased serum transaminase levels preceded surgery; anesthesia without enflurane for drainage of a pelvic abscess (postoperative day 16) also was followed by increased serum transaminases.
FDA Case #2	Insufficient data (half-page FDA form).
FDA Case #3	Peritonitis with subphrenic and subhepatic abscesses; septicemia; shock; anemia; transfusion of two units of blood; hyperalimentation.
FDA Case #4	Symptom onset three weeks after surgery; congestive heart failure; cardiogenic shock; cardiac arrest.
FDA Case #9	Symptom onset 31 days after surgery, for which two units of blood were used.
FDA Case #10	Insufficient data; the record appears to suggest possible liver injury prior to surgery with positive hepatitis B antigen.
FDA Case #12	Prior diagnosis of cirrhosis; perioperative hypotension and hypoxemia.
FDA Case #13	Insufficient data.

[a] Listed as they appeared in Lewis et al. (12)

their features were consistent with the syndrome associated with halothane-induced hepatitis. That is, those reporting these cases reasoned that enflurane and halothane exerted an analogous effect on the liver. Clearly, halothane and enflurane have similar characteristics. Both compounds are halogenated with fluorine and chlorine. Both are potent inhaled anesthetics that can produce profound cardiorespiratory depression. Also, both have similar pharmacokinetic characteristics.

But proof by analogy is the weakest way of demonstrating an association (21). The argument is weakened further by the tenuousness of the evidence of halothane-induced hepatitis. Venning (22) notes that the concerns expressed about halothane took 13–19 years to support. In addition, Venning classifies that evidence as being extremely weak. It is difficult to differentiate halothane-induced hepatitis from viral hepatitis (16). These observations are not intended to suggest that we believe that halothane is not hepatotoxic in rare patients. However, the weakness of the evidence for halothane makes any link with enflurane questionable.

The argument by analogy also founders because enflurane is basically different from halothane in properties thought important to hepatotoxicity. A current theory of halothane hepatotoxicity holds that liver injury results from halothane biodegradation: the metabolites of halothane either attack liver cells directly (23–27) or cause injury indirectly by inducing an allergic response (28,29). If this theory is correct, then enflurane would be unlikely to cause injury in the same manner as halothane. Fifteen to 20% of the halothane taken up by a human being can be recovered as urinary metabolites (30), whereas only 2.4% of the enflurane taken up can be recovered as urinary metabolites (31). Halothane undergoes reductive metabolism (23–27), but enflurane does not (32). Reductive metabolism of halothane produces free radicals, whereas under the same conditions, no free radicals are produced from enflurane (33). Halothane is broken down to toxic compounds by soda lime (34,35) or ultraviolet light (36), but enflurane is not (37). Thus there are few, if any, parallels in the metabolism of halothane and enflurane. If no parallels exist for this postulated mechanism of halothane-induced hepatitis, why should one exist regarding a syndrome?

As noted previously, one theory of anesthetic-induced liver injury holds that such injury results from sensitization either to the anesthetic itself (a very unlikely occurrence) or to a reactive metabolite of the anesthetic that acts as a hapten. If this theory is correct, the incidence of injury should increase with repeated exposure to anesthesia (especially the third or fourth exposure). Such appears to be the case with halothane but not with enflurane (38,39). The theory also would predict an increase in the incidence of injury several years after the commercial release of an anesthetic, because repeated exposures to the anesthetic would become more frequent several years after release. Again, this appears to be the case with halothane but not with enflurane (Fig. 2).

The incidence of reported cases of hepatic injury after enflurane actually has decreased because the

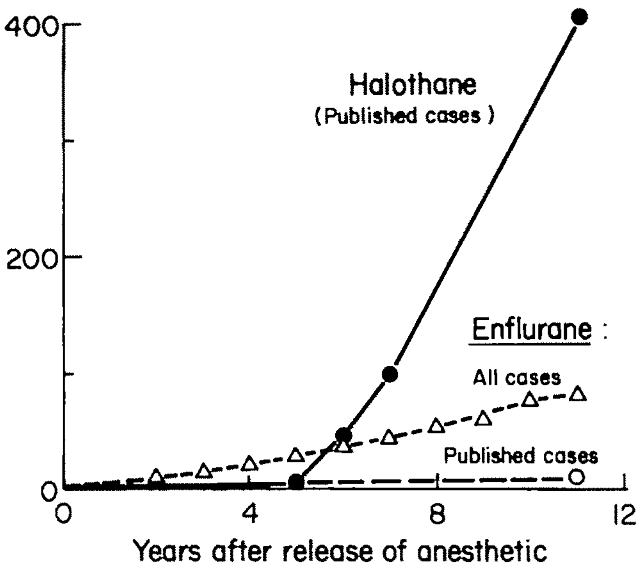

Figure 2. Total reported cases from release of halothane or enflurane to date of liver injury or jaundice. The number of published reports of hepatic injury after halothane anesthesia dramatically increased about five years after the introduction of halothane (●) into clinical practice. No such upturn has appeared in the 11-year period following the release of enflurane (△ and ○). The halothane data are taken from Zimmerman (39), whereas the enflurane data are taken from references (2–11) and from the Food and Drug Administration and the Armed Forces Institute of Pathology.

number of reported cases has not increased in proportion to the increase in use of enflurane. Thus for the period from 1972 to 1978, 46 cases were reported and 18.0 million anesthetics were given, for an incidence of 2.6 cases per million anesthetics. For the period from 1979 to 1982, 38 cases were reported and 25.1 million anesthetics given, for an incidence of 1.5 cases per million anesthetics. Similarly, no significant increase in the incidence is seen if only unexplained (possible) cases are examined: for the period from 1972 to 1978, the incidence was 0.33 cases per million anesthetics; whereas for the period from 1979 to 1982, the incidence was 0.36 cases per million.

Examination of patients for the 12 syndrome variables did not reveal a significant difference between the possible and the unlikely groups. This is not surprising, because the average incidence was higher in the unlikely group for five of the 12 variables (fever as a presenting sign, rash, bilirubin level higher than 2.5 mg/dl, centrilobular necrosis, and death), and for one item (jaundice observed by the attending physician) there was no difference between the groups.

However, the selection of certain variables from Table 1 easily permits the construction of syndromes that significantly favor either the unlikely or the possible group. For example, the unlikely group would score significantly higher ($P < 0.001$) if the syndrome items consisted of the following: peak temperature greater than 40°C; the presence of renal failure; an LDH value more than ten times (1490 IU) the normal value; major cavity surgery; congestive heart failure; hypoxia; evidence of infection; and centrilobular necrosis. The possible group would score significantly higher ($P < 0.001$) if the syndrome variables consisted of the following: female gender; a history of allergy; prior anesthesia with a halogenated anesthetic; symptoms within five days; an SGOT value more than ten times (370 IU) the normal value; nausea; and chills. Such a retrospective examination may be used to construct a study that would evaluate factors that might predict the development of injury to the liver with enflurane. But such an examination cannot legitimately be applied to the present data to make such a determination.

Although we examined the same material, our conclusions differed from those of Lewis et al. We had access to eight more cases; that difference, however, is probably inconsequential. We also differed in our assessment of the number of patients whose liver injury was unexplained and therefore possibly caused by enflurane. Lewis et al. selected 24 cases, whereas we selected only 15. We agreed with Lewis et al. regarding 13 of the cases selected, but disagreed on 11. Of the 11, three had too little information to allow us to form a judgment. We excluded the remaining eight patients for one of two reasons: other causes of liver injury seemed apparent or we applied criteria previously suggested by one of Lewis' coauthors. For example, Zimmerman wrote: "Rarely (5 percent of patients) more than three weeks elapses between the surgical procedure and the appearance of jaundice, an interval so long as to make such cases diagnostically suspect" (40). Two of the eight patients demonstrated the first signs of liver injury 20 or more days after anesthesia. The patient listed by Lewis et al. as FDA Case #8 demonstrated such signs 31 days after surgery. Our rationale for excluding the 11 cases included by Lewis et al. is given in Table 2.

The data we assembled allow us to estimate the minimum incidence of unexplained liver injury after enflurane anesthesia. Anaquest (the manufacturer of enflurane) estimates that approximately 43.1 million anesthesias were given with enflurane in the period from 1972 through 1982. This estimate and the 15 unexplained cases of injury represent a minimum incidence of one per 2.9 million enflurane anesthetics. The true incidence is clearly higher. A closer approximation may be obtained if we confine our estimate to unexplained cases of severe injury or death. An instance of severe unexplained injury is more likely to be published or brought to the attention of the FDA (usually through a report to the drug manufacturer) or the AFIP.

The greater likelihood of reporting is suggested from the data accumulated in the National Halothane Study (16). Of the seven cases of severe unexplained injury (hepatic necrosis and death) reported to follow the administration of halothane, six were known (i.e., had been reported) prior to the initiation of the study. In the present series, there were six cases of severe unexplained injury (including two deaths), for an incidence of 0.14 cases per million enflurane anesthetics. Parallel data from the National Halothane Study consist of seven cases after an estimated 254,896 administrations, for an incidence of 27.5 cases per million halothane anesthetics. That is, the estimate of the incidence for halothane-induced injury is more than 200 times greater than the estimate for enflurane-induced injury. Furthermore, the incidence for halothane is underestimated, because it is based on autopsy examination: only 60.4% of the patients who died underwent abdominal necropsy; and, in addition, no estimate could be made regarding the number of patients who had severe injury but survived.

Perhaps at issue is the question, "How many anecdotal cases of unexplained liver injury would be required to document a causal relationship (an association) between the administration of enflurane and injury?" No number of anecdotal cases can prove an association in the absence of a comparison group. The incidence of anecdotal cases may be no greater than the incidence that would appear in the absence of enflurane. Furthermore, there is no feasible way of defining that baseline (some anesthetic would have to be substituted for enflurane, and it could be argued that the substituted anesthetic altered the natural incidence). Therefore, we cannot determine whether anecdotal reports show an association.

If enflurane is not a hepatotoxin, how then may we account for the possible cases? Although no conclusive answer can be supplied, it should be noted that anesthesia and surgery themselves can stress the liver. Some anesthetic agents are not commonly thought of as hepatotoxins, yet evidence points to them as being as likely as, or more likely than, enflurane to injure the liver or to predispose to injury. Thiopental (41–45), nitrous oxide (46–49), and narcotics (45,50) are examples of such agents. All patients in the possible group were given nitrous oxide, 73% were given a barbiturate for induction of anesthesia, and 80% were given a narcotic perioperatively. Finally, non-A, non-B hepatitis clearly is a major potential cause of unexplained postoperative liver injury (51), and hepatitis B virus can be present in the livers of patients who have negative serum tests for hepatitis B surface antigen (52). The authors of the latter investigation suggest that "multiplication of HBV (hepatitis B virus) may occur in the absence of any conventional serologic marker for HBV." Non-A, non-B hepatitis was involved in at least one case of perioperative liver injury in which enflurane was suggested as a possible causal factor (6).

The natural incidence of non-A, non-B hepatitis may confound any study of the incidence of hepatitis secondary to the administration of enflurane. As noted above, the incidence of hepatitis secondary to enflurane probably is extremely low. In contrast, the incidence of non-A, non-B hepatitis in patients undergoing surgery who do not receive blood is relatively high. Stevens et al. (53) found that 41 of 1235 such patients (3.3%) developed non-A, non-B hepatitis. Given this background "noise," it would be difficult to define the impact of a factor that added one patient in tens or hundreds of thousands of patients.

What can we conclude? First, in the rare patient, unexplained severe liver damage follows enflurane anesthesia. Lewis et al. suggest that this demonstrates a causal relationship. Furthermore, such reports might represent the tip of an iceberg. We argue that the known incidence is far too small to suggest an association and that other causes cannot be excluded.

Second, we agree with Lewis et al. that if enflurane is a hepatotoxin, its toxicity is far less than that attributed to halothane.

Third, a mechanism by which enflurane might act as a hepatotoxin is difficult to describe and to support with experimental evidence.

Fourth, we believe that no specific histologic picture exists in the patient who develops hepatitis after enflurane anesthesia. If centrilobular necrosis is appropriate as a designation of this type of injury, it is not evident in the available material. However, our failure to find a consistent histologic picture might be the result of a sampling or timing error.

Fifth, we do not find valid evidence for a syndrome similar to that which supposedly exists for halothane-induced hepatitis.

Why do we insist on better proof before a causal relationship is declared? One concern is that the inappropriate assertion of a causal relationship impugns the reputation and may decrease the application of a useful therapeutic agent. That is, it may deny the use of enflurane in patients in whom it would be an optimal agent. A second concern is that the acceptance of a causal relationship provides a reason to stop looking for other causes.

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ANESTH ANALG
1986;65:31–6

Severe Preeclampsia:

Hemodynamic Effects of Lumbar Epidural Anesthesia

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NEWSOME LR, BRAMWELL RS, CURLING PE. Severe preeclampsia: hemodynamic effects of lumbar epidural anesthesia. Anesth Analg 1986;65:31–6.

The hemodynamic effects of lumbar epidural anesthesia (LEA) were evaluated in 11 patients with severe preeclampsia. All patients were receiving magnesium sulfate upon entry into the study. Hemodynamic measurements were obtained before and after LEA, at delivery, and 2 hr postpartum. Lumbar epidural anesthesia significantly reduced mean arterial pressure from 121.4 mm Hg to 97.7 mm Hg, without altering cardiac index, pulmonary vascular resistance, central venous pressure (CVP), or pulmonary capillary wedge pressure (PCWP). There was a slight but statistically insignificant decrease in systemic vascular resistance from 1078 to 900.7 dynes·sec·cm^{-5}. Cardiac index and left ventricular stroke work index were elevated in these patients, suggesting hyperdynamic left ventricular function. There was poor correlation between PCWP and CVP in several patients. We conclude that LEA may be used safely in severe preeclamptic patients and that pulmonary arterial catheters may help guide appropriate therapy in preeclamptic patients with cardiac failure or oliguria refractory to modest fluid challenges.

Key Words: ANESTHESIA—obstetric. ANESTHETIC TECHNIQUES—epidural.

Preeclampsia continues to represent a significant cause of morbidity and mortality in 5–10% of all pregnancies (1). The pathophysiology of preeclampsia can involve virtually every organ system, and in extreme cases cardiac decompensation may occur (2,3). Several clinical reports citing the hemodynamic profiles of severely preeclamptic patients vary considerably in the type of anesthesia employed and in the use of vasoactive medications prior to invasive hemodynamic determinations (3–7). In the present study we examined the hemodynamic effects of lumbar epidural anesthesia (LEA) in severe preeclamptic patients not receiving vasodilator treatment.

Materials and Methods

After obtaining approval from the Human Investigations Committee (HIC), peripartum hemodynamic measurements were collected in eleven patients with severe preeclampsia as defined by the criteria of the American College of Obstetricians and Gynecologists (8). All patients were monitored with a lead II electrocardiogram, a Foley catheter to measure urinary output, a 20-gauge percutaneous radial artery catheter, and an Edwards model 93A-131H-7F heparin-coated flow-directed pulmonary artery catheter inserted via the basilic (n = 7) or femoral vein (n = 4). (The HIC believed that this patient population would be more tolerant of peripheral venipunctures.) Hemodynamic measurements included systemic and pulmonary artery systolic and diastolic pressures, cardiac output, central venous pressures (CVP), and pulmonary capillary wedge pressures (PCWP). Cardiac indices (CI) and pulmonary and systemic vascular resistances (PVR and SVR) were calculated. Intravascular pressures were measured with Statham transducers, and cardiac output (CO) determinations were performed in triplicate via the thermodilution method. All measurements were obtained in the interval between contractions with the patients positioned in the left lateral tilt position. All patients received LEA after verification of normal coagulation profiles and after intravenous administration of up to 1000 cc of lactated Ringer's solution to maintain the PCWP between 8 and 12 mm Hg. The six patients who delivered vaginally received 5–10 ml of bupivacaine, 0.125%, without epinephrine for analgesia. The five patients who underwent cesarean section received 18–25 ml of bupivacaine, 0.5%, without epinephrine to provide loss of sensation to the T4–T6 sensory level. All patients were receiving $MgSO_4$ infusions at a rate of 1 g·hr^{-1}

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Table 1. Individual Patient Data and Laboratory Findings of Severe Preeclamptic Patients upon Presentation

Patient number	Maternal age (yr)	Gestational age (weeks)	MAP mm Hg	HR (beats/min)	Hgb	Hct	Mode of delivery	Platelet count × 10^9/L	Apgar scores after 1 min	Apgar scores after 5 min	Proteinuria
1[a]	20	43	125	103	13.2	39.2	Cesarean	206	8	9	1+
2	21	—	115	119	—	36	Vaginal	130	6	8	—
3[a]	19	41	130	136	—	41.2	Vaginal	195	8	9	3+
4	16	37	113	106	11.8	35.0	Vaginal	295	8	8	2+
5[a]	14	39	136	120	—	36	Cesarean	102	8	9	2+
6[a]	16	41	120	113	12.5	37.6	Vaginal	183	8	8	3+
7[a]	16	35	120	108	13.8	41	Vaginal	185	4	9	4+
8[a]	30	29	126	126	13.1	39.3	Cesarean	134	4	8	2+
9	28	35	120	80	12.1	35.1	Vaginal	107	3	8	4+
10[a]	24	35	115	72	—	33.9	Cesarean	252	8	9	2+
11	19	—	112	123	—	—	Cesarean	136	6	9	—

[a] Received hydralazine (5–10 mg intravenously) after lumbar epidural anesthesia, in the post partum period, or both.

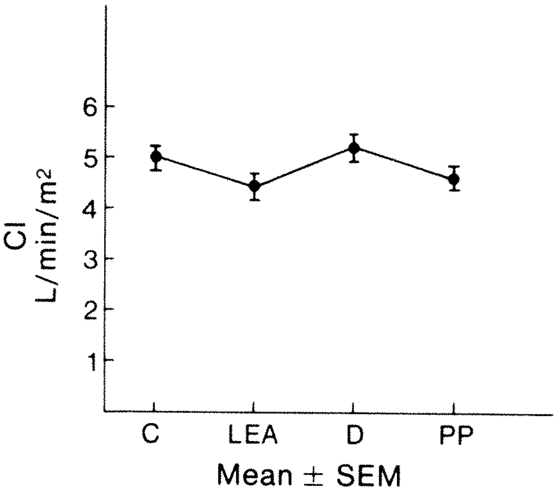

Figure 1. Hemodynamic data from severely preeclamptic patients at control (C), after lumbar epidural anesthesia (LEA), at delivery (D), and 2 hr postpartum (PP). Data expressed as mean ± SEM. Statistical significance designated by *($P \leq 0.05$)

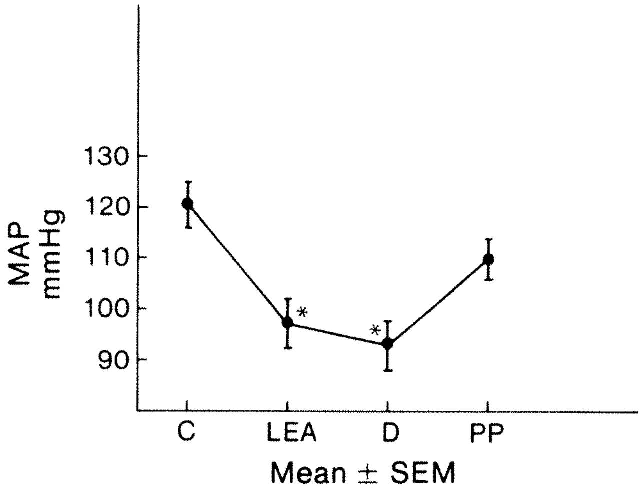

Figure 2. Hemodynamic data from severely preeclamptic patients at control (C), after lumbar epidural anesthesia (LEA), at delivery (D), and 2 hr postpartum (PP). Data expressed as mean ± SEM. Statistical significance designated by *($P \leq 0.05$)

after an intravenous loading dose of 4 g given over 5 min. None of the patients received additional vasodilator therapy prior to initial hemodynamic determinations. Seven patients received hydralazine, 5–10 mg intravenously, after LEA, post partum (PP), or both, for blood pressure control. Hemodynamic measurements were obtained before (C), and after LEA, at delivery (D), and 2 hr PP. Urinary output was maintained at 0.5 ml·kg^{-1}·hr^{-1} or greater by maintaining PCWP between 8–12 mm HG when necessary. There were no complications associated with the use of the pulmonary artery catheters. All newborn infants had a 5-min apgar score ≥ 8.

Statistics

Results are expressed as mean ± SEM. The significance of differences from control values was determined by analysis of variance with Tukey's method of multiple comparisons, assuming $P < 0.05$ to be statistically significant (9). Regression analysis for the correlation of CVP and PCWP during the peripartum period was also performed (10).

Results

The mean age of the severely preeclamptic patients was 20 yr (range 14–30), and the mean gestational age

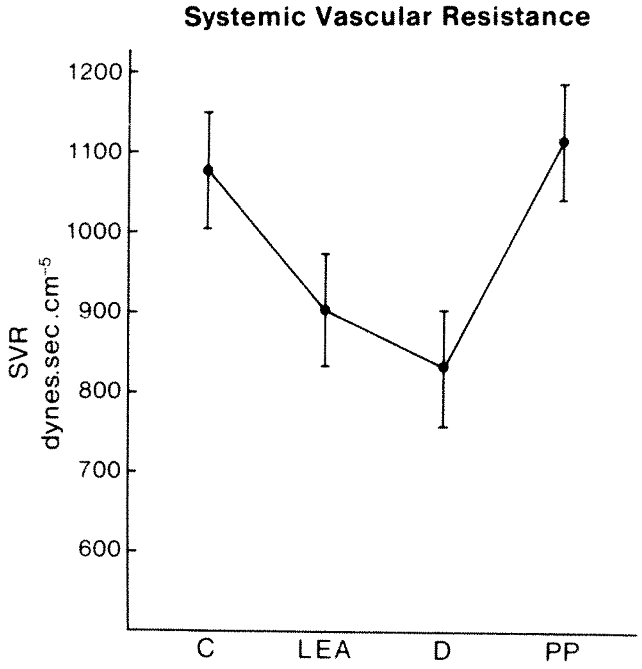

Figure 3. Hemodynamic data from severely preeclamptic patients at control (C), after lumbar epidural anesthesia (LEA), at delivery (D), and 2 hr postpartum (PP). Data expressed as mean ± SEM. Statistical significance designated by *($P \le 0.05$)

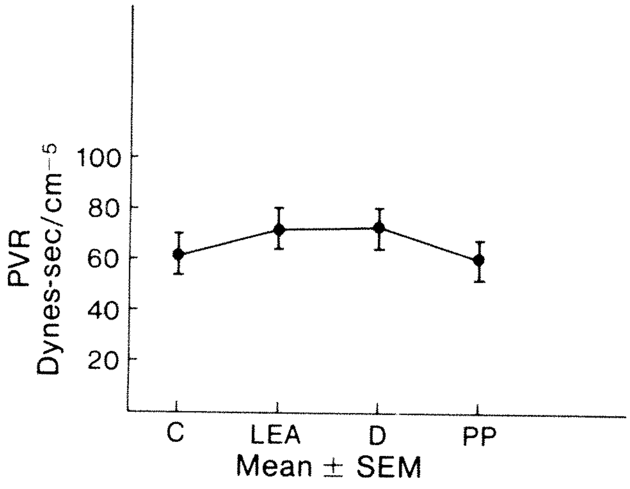

Figure 4. Hemodynamic data from severely preeclamptic patients at control (C), after lumbar epidural anesthesia (LEA), at delivery (D), and 2 hr postpartum (PP). Data expressed as mean ± SEM. Statistical significance designated by *($P \le 0.05$)

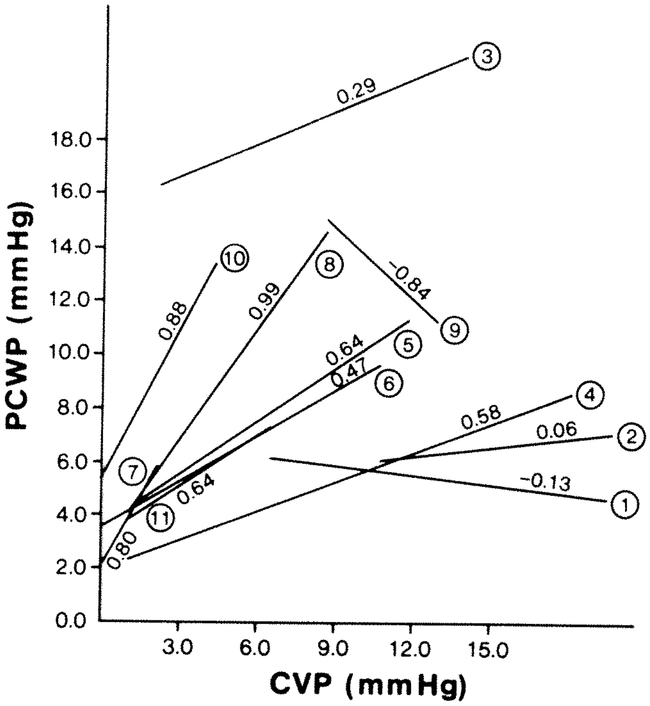

Figure 5. Regression lines and correlation coefficients for 11 patients with severe preeclampsia. PCWP and CVP were poorly correlated in several patients, and the dispersion of data around individual regression lines was large.

in weeks was 37 (range 29–43). Individual patient data and laboratory results of the severe preeclamptic patients are presented in Table 1.

Mean cardiac index prior to LEA was 5.0 L·min^{-1}·m^2 and did not change after LEA, after delivery, or in the postpartum period (Fig. 1). Mean arterial pressure (MAP) was significantly reduced from 120 mm Hg to 97 mm Hg with the institution of LEA, and it remained in that range until the postpartum period (Fig. 2). Systemic vascular resistance was within normal limits prior to LEA, with a mean value of 1078 dynes·sec·cm^{-5}. Lumbar epidural anesthesia resulted in a slight (statistically insignificant) decrease in SVR (900.7 dynes·sec·cm^{-5}) that persisted throughout the delivery period (Fig. 3). Both MAP and SVR returned toward control values in the postpartum period. Pulmonary vascular resistance was normal before LEA (62 dynes·sec·cm^{-5}) and was not affected by LEA, delivery, or in the postpartum period (Fig. 4). There were no statistically significant changes in PCWP or CVP during the four measured intervals.

Regression analysis for the correlation of CVP with PCWP in the peripartum period showed poor correlation between these variables. Four patients showed extremely poor correlation with correlation coefficients of −0.13, 0.06, 0.29, and −0.84. The dispersion of data points around the individual regression lines was large in these patients, again illustrating poor correlation between these variables (Fig. 5).

Seven patients had hyperdynamic left ventricular function compared to normal, nonpregnant patients. However, two patients had depressed left ventricular function. One of these patients was admitted to our hospital with pulmonary edema. After initially im-

Table 2. Hemodynamic Profile of a Severe Preeclamptic Patient with Pulmonary Edema

	C	LEA	D	2 hr PP	10 hr PP[a]	12 hr PP
MAP (mm Hg)	130	77	80	110	94	92
CO (L/min)	6.0	7.6	7.4	4.8	3.5	6.7
SVR (dynes·sec·cm^{-5})	1600	785	832	1600	1988	1074
PCWP (mm Hg)	19	17	19	17	28	16
CVP (mm Hg)	7	2	3	3	7	1

[a] Afterload reduction therapy with intravenous hydralazine instituted.
Abbreviations: C, control; LEA, after lumbar epidural anesthesia; D, delivery; PP, post partum.

proving with only the use of LEA, this patient again developed left ventricular dysfunction in the postpartum period, characterized by elevated PCWP, low CO, and elevated SVR. The institution of afterload reduction therapy with hydralazine resulted in a dramatic improvement in the clinical status of this patient with a return of CO toward normal levels and a decrease in SVR (Table 2).

Discussion

Rafferty and Berkowitz (4) reported three patients with severe preeclampsia who received general anesthesia after a rapid sequence induction and intubation for cesarean section. All three patients received hydralazine boluses and $MgSO_4$ infusions prior to initial invasive hemodynamic determinations. They found elevated cardiac output (9–14 L·min^{-1}), low systemic vascular resistance, normal pulmonary artery pressure, and hyperdynamic left ventricular function (3). Of interest is the observation that one patient had an increase in MAP from 120 mm Hg to 173 mm Hg with intubation.

Rolbin et al. evaluated hemodynamic function in four patients with severe preeclampsia (11), three of whom had received general anesthesia and one LEA for delivery. In addition, three of the four had received hydralazine and $MgSO_4$ prior to hemodynamic determinations, and these patients had significantly higher cardiac output and lower systemic vascular resistance than the patient who did not receive hydralazine.

Hemodynamic observations in 10 severely preeclamptic patients receiving only $MgSO_4$ prior to initial measurements were reported by Benedetti et al. (5). All of their patients received either inhalation analgesia or narcotics for pain relief. They found elevated cardiac outputs with a mean value of 7.4 L·min^{-1} and a mean SVR of 1332 dynes·sec·cm^{-5} with poor correlation between CVP and PCWP in three out of nine patients. Left ventricular function was characterized as hyperdynamic, and CO did not significantly change at delivery or in the postpartum period.

The effect of LEA on CO in severe preeclamptic patients has been evaluated by Graham and Goldstein (6). All ten of their patients received intravenous $MgSO_4$ infusions and hydralazine in 5–10-mg boluses "when needed" to control blood pressures. Cardiac output during labor and before LEA was 8.8 L·min^{-1}, which was not significantly changed by LEA. They found, however, a significant increase in CO 15 min after delivery with a mean value of 11.4 L·min^{-1}, which returned toward baseline over the next hour. All their measurements were taken with the patients in the supine position. In addition they made no mention of filling pressures, pulmonary vascular resistance, or SVR.

Considering the heterogeneity of anesthetic techniques and the use of vasodilators given prior to initial invasive hemodynamic measurements, it is not surprising that there are conflicting findings in the above clinical studies. Hydralazine, an antihypertensive agent, is a direct vasodilator of vascular smooth muscle. The resulting decrease in afterload often results in a decrease in SVR and a concomitant increase in CO (12). It is understandable that patients receiving hydralazine may not be truly representative of the natural preeclamptic state. This point is illustrated in the prelabor hemodynamic observations of third trimester preeclamptic patients reported by Groenendijk et al. (13). Their patients initially had low cardiac indices (2.75 L·min^{-1}·m^{2}), high SVR (1943 dynes·sec·cm^{-5}), and low PCWP (3.3 mm Hg). Volume expansion and vasodilation with hydralazine resulted in a significant ($P < 0.01$) increase in CI to 4.40 L·min^{-1}·m^{2} and reduction in SVR to 947 dynes·sec·cm^{-5}.

Magnesium sulfate also has vasodilatory actions in addition to its anticonvulsant properties (14). When given as a bolus it has been shown to cause a significant reduction in blood pressure in hypertensive patients in addition to controlling the hypertensive responses to intubation in preeclamptic patients (15,16). All of our patients were receiving $MgSO_4$ upon entry into the study because we could not justify delaying treatment in these critically ill patients in order to obtain truly baseline hemodynamic measurements.

Cotton et al. recently obtained such measurements in five severely preeclamptic patients (17). They reported a slight transient increase (12.5%) in CI, and a significant ($P < 0.01$) decrease in MAP after a 4-g bolus of $MgSO_4$ given over 15 min.

We were able to obtain hemodynamic measurements in our patients without any of them receiving hydralazine. Our hemodynamic data were, therefore, similar to those reported by Benedetti et al. (5) with high CO and normal SVR in contrast to the high CO and low SVR reported in the series of Rafferty et al. (4) and Rolbin et al. (11) where hydralazine had been used. The low cardiac indices reported in Groenendijk's (13) series of patients may be attributed to the fact that his patients were not in labor. Similar to the findings of Graham and Goldstein, we found that epidural anesthesia had no effect on CO during labor, delivery, or 1–2 hr postpartum.

The poor correlation between CVP and PCWP in our series of severely preeclamptic patients was consistent with the findings of Benedetti et al. (5). Central venous pressure both underestimated and overestimated PCWP in a significant number of patients in both series. This lack of correlation does not necessarily mean that all severely preeclamptic patients should be monitored with a pulmonary artery catheter. The presence of pulmonary edema in a severely preeclamptic patient does represent an indication for a pulmonary artery catheter for optimum perioperative management. Patients with oliguria refractory to modest fluid challenges, associated with a normal CVP, or both, may also benefit from a more accurate assessment of left-sided filling pressures. It is important to note that the poor correlation between CVP and PCWP turned out to be an incidental finding in three out of the four patients because there were no clinical signs or symptoms that would have caused us to suspect this abnormality. Therefore, although pulmonary artery catheters are not essential in the management of every severely preeclamptic patient, knowledge of this potentially poor correlation between CVP and PCWP may be important for those patients with diagnostic or therapeutic uncertainties.

One common theme in the majority of the clinical reports of severe preeclamptic patients is the existence of hyperdynamic left ventricular function defined as the relationship between PCWP and left ventricular stroke work index. It should be noted that this hyperdynamic left ventricular function is in comparison to normal nonpregnant patients. There is, understandably, a scarcity of hemodynamic data obtained from invasive monitors in normal pregnant patients.

Bader and Braunwald have reported such data in normal pregnant patients obtained via cardiac catheterization at rest and exercise with calculation of CO using the Fick principle (18). When comparing their data in normal pregnant patients with ours, we find that two out of four of the normal pregnant patients from Bader and Braunwald's series also had hyperdynamic left ventricular function, as compared to seven out of 10 of our severely preeclamptic patients (Fig. 6). Although it appears that severely preeclamptic patients do indeed have hyperdynamic left ventricular function, it is also quite possible that pregnant patients in general may have hyperdynamic ventricular function when compared to their nonpregnant counterparts. This should not be surprising because it is known that CO is normally elevated in pregnancy (19).

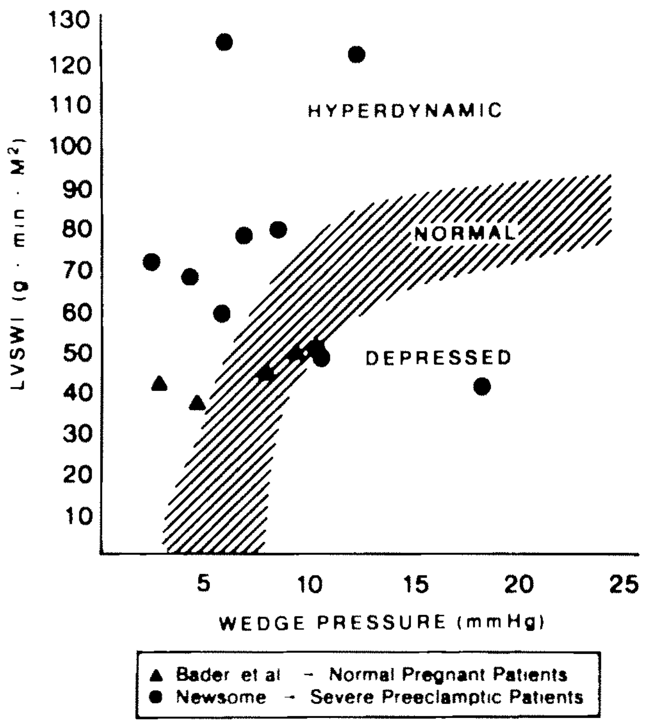

Figure 6. Comparison of ventricular function measurements (left ventricular stroke work index [LVSWI] versus PCWP) in severe preeclamptic patients and in normal pregnant patients.

The contribution of this elevated left ventricular function to the hypertension in these patients is unclear. Specifically, should negative inotropic agents be employed for the treatment of hypertension in those severe preeclamptic patients with hyperdynamic left ventricular function? For example, patients with elevated cardiac indices and low systemic vascular resistances may be refractory to additional vasodilator therapy and may respond quite favorably to negative inotropic drugs like β-blockers and calcium channel blockers. Norris et al. found that verapamil resulted in a decrease in blood pressure without a concomitant decrease in uterine blood flow in hypertensive sheep (unpublished observation). The possibility of negative inotropic interventions with either β-blockers or calcium channel blockers in severe preeclamptic patients certainly deserves further investigation (20).

In conclusion, contrary to the opinion of Pritchard et al. (21), LEA may be used safely in severely preeclamptic patients without adversely affecting CO and may facilitate control of blood pressure. Severely preeclamptic patients may present clinically with a wide spectrum of hemodynamic profiles. Treatment of preeclamptic patients with magnesium sulfate and other vasodilators may also alter hemodynamics. CVP correlated poorly with PCWP in several severely preeclamptic patients in our series, and therefore, in patients with cardiac failure or oliguria refractory to modest fluid challenges, the use of pulmonary artery catheters may allow titration of therapy to physiologic measured endpoints.

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Pulmonary Macrophage Mobilization in Cigarette Smoke-Exposed Mice after Halothane Anesthesia

El-Sayed Hegab, PhD, MD, and Daniel H. Matulionis, PhD

HEGAB ES, MATULIONIS DH. Pulmonary macrophage mobilization in cigarette smoke-exposed mice after halothane anesthesia. Anesth Analg 1986;65:37–45.

The effects of halothane anesthesia on pulmonary tissue and lung macrophage population were evaluated in normal and in C57BL/6 mice exposed to cigarette smoke twice daily for one year. Morphologic assessment of pulmonary tissue revealed no lung abnormalities that could be attributed solely to halothane anesthesia. However, in animals that were exposed to smoke and subsequently halothane anesthesia, airways cilia were shorter in stature and fewer in number. Disorientation of ciliary basal bodies was also observed. Airway macrophages in smoke-exposed animals subjected to halothane anesthesia were, for the most part, larger in size and contained more lysosomes and inclusions than phagocytes in airways of all other animals. Smoke inhalation alone caused a significant increase in number of lung parenchymal macrophages when compared to the number of these cells in sham-treated and control animals. However, the total macrophage population was significantly greater in lungs of smoke-exposed mice 48 hr after anesthesia than in lungs of smoke-exposed mice not subjected to halothane anesthesia and to those of sham-treated and control animals that were or were not exposed to the anesthetic. Airway macrophage numbers were significantly elevated in smoke-exposed mice 48 hr after halothane when compared to those of all other groups. Conversely, the number of parenchymal macrophages decreased in lungs of these mice. It was proposed that in smoke-exposed mice subjected to halothane anesthesia, ciliary function is impaired and phagocytes are mobilized from alveoli into the airways.

Key Words: ANESTHETICS, VOLATILE—halothane. LUNG—cigarette smoke and anesthesia.

Pulmonary complications are a major cause of morbidity and death after anesthesia and surgery (1–5). Cigarette smoking significantly increases the risk for development of these complications by 2- to 6-fold (3,4,6–10). However, the contribution of anesthesia alone to the pathophysiology of pulmonary complications is not clear. Thus the present study utilizing C57BL/6 mice was designed to determine whether inhalational anesthesia (halothane) causes morphologic pulmonary abnormalities and to assess the response of the lung macrophage system after anesthesia in smoke-exposed and normal animals. The phagocytic system was chosen for evaluation because these cells are of primary importance in maintaining the sterility and normal function of the lungs (11,12) and the system is known to be affected markedly by inhalation of smoke (13–16).

Materials and Methods

Ninety-five C57BL/6 adult male mice previously quarantined for 10 days were studied. During quarantine and the course of the experiment, animal health was monitored as described earlier (17). The animals were divided into three groups: 35 smoke-exposed mice; 35 sham-treated animals (i.e., manipulated similarly to smoke-exposed mice except that room air was substituted for cigarette smoke); and 25 controls (not exposed to smoke or sham treatment) (Table 1). At the time smoke exposure began, all animals were 12–14 weeks of age. Mice were exposed to smoke from 2A1 Reference cigarettes (University of Kentucky) in the Kentucky smoking machines (18) twice daily for one year. Smoke exposure, sham treatment, housing, and other experimental conditions of the animals have been detailed earlier (19,20).

At the end of the 1-yr smoke exposure period, 14 of surviving (each) smoke-exposed, sham-treated, and control animals (Table 1) were subjected to halothane

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Table 1. Treatments and Number of Animals Used

	Number of animals					
Treatment[a]	At onset of experiment	Deaths over 1 year	Determination of minimum anesthetic requirements	Exposure to halothane	Deaths during halothane exposure	Sacrificed
Smoke-exposed	35	8				5
Sham-treated	35	7				5
Control	25	2				5
Smoke + Hal.			8	14	3	
Sham + Hal.			9	14	2	
Cont. + Hal.			4	14	1	
Sm. + Hal. 24 hr						5
Sm. + Hal. 48 hr						5
Sh. + Hal. 24 hr						5
Sh. + Hal. 48 hr						5
Cont. + Hal. 24 hr						5
Cont. + Hal. 48 hr						5

[a] Abbreviations: Sm. or Smoke, smoke-exposed; Sh. or Sham, sham-treated; Hal., halothane anesthesia; Cont., control; hr, hours.

(2-bromo-2-chloro-1,1,1-trifluroethane) anesthesia by placing the animals into a 2.5-L capacity clear plexiglass chamber. A Fluotec halothane vaporizer (Cyprane North America Inc., Tonawanda, NY 14150) was connected to the chamber, and 100% O_2 was used as a carrier at a flow rate of 3 L/minute. Minimum anesthetic requirement of halothane was determined in 8 smoke-exposed, 9 sham-treated, and 4 control animals (Table 1) according to the method of Goldstein et al. (21). A delivered halothane concentration of 1.2% from a calibrated Fluotec vaporizer prevented 50–70% of the animals from movement in response to tail clamping and was considered to approximate minimum alveolar concentration (21). Induction of anesthesia was achieved using 1.6% delivered concentration of halothane in 100% oxygen, and the chamber was sealed. After the first 15 min, the concentration of delivered halothane was reduced to 1.2% throughout the 2-hr period of anesthesia. The temperature in the chamber was maintained at approximately 37°C during anesthesia and recovery. Animals were observed closely for 4 hr after recovery from anesthesia. Mice were not subjected to smoke exposure or sham treatment on the afternoon of the day of halothane administration. Five (each) smoke-exposed, sham-treated, and control mice were sacrificed 24 and 48 hr after the onset of halothane anesthesia (Table 1). Five (each) additional smoke-exposed, sham-treated, and control animals that were not exposed to halothane anesthesia (Table 1) were sacrificed on the day the halothane was administered to the other mice.

Mice were sacrificed by intraperitoneal injections (80 mg/kg) of sodium pentobarbital (Butler Co., Columbus, OH 43228) and exsanguinated by cutting the abdominal aorta. The cephalic two-thirds of the left lung was then immediately excised, fixed by immersion in 10% neutral buffered formalin, and prepared for light microscopy by methods described earlier (17). To assess whether differential shrinkage, or collapse of lungs, or both occurred after pneumothorax and tissue processing as a result of different treatments of animals, area of lung sections from all mice, cut at identical locations, was calculated using an image analysis system (Zeiss Video Plan Image Analysis System, Carl Zeiss Inc., Thornwood, NY). Tissue for electron microscopy was prepared by methods described elsewhere (17,22).

The number of macrophages in alveolar spaces and septa (parenchymal macrophages) and those in bronchi and bronchioles (airway macrophages) was determined (blindly) from tissue prepared for light microscopy as follows. Parenchymal macrophages in each animal were counted in ten randomly selected fields of tissue measuring 0.028 mm^2. Each field was composed of alveolar tissue only; bronchi, bronchioles, large vessels, and connective tissue regions were excluded from the sampling. Airway macrophages were determined in four areas measuring 0.212 mm^2, which covered approximately 80–90% of the lung section. Different areas used to count parenchymal and airway macrophages reflect the need for higher magnification to identify the former than the latter. Subsequently, the number of parenchymal macrophages (PM) was equated mathematically to reflect the area evaluated to obtain airway macrophage (ARM) counts by calculating: $PM_m \times (ARM_a/PM_a)$ where PM_m is the raw mean of PM and ARM_a and PM_a the unit areas used

Table 2. Animal Weights in Grams[a]

Animal groups	Beginning of treatment[b]	Termination of treatment[c]	24 hr post halothane[d]	48 hr post halothane[d]
Control	25.2 ± 0.4	32.7 ± 1.9	32.9 ± 0.6	33.1 ± 1.9
Sham-treated	24.6 ± 0.4	26.2 ± 0.8	29.0 ± 1.2	27.5 ± 0.5
Smoke-exposed	24.9 ± 0.4	25.9 ± 0.8	25.8 ± 0.8	25.9 ± 0.5

[a] Mean ± SEM.
[b] $n = 20$, animals 12–14 weeks of age.
[c] $n = 20$, animals 64–66 weeks of age.
[d] $n = 5$, animals 64–66 weeks of age.

Table 3. Area of Lung Sections Used to Count Lung Parenchymal and Airway Macrophages

Treatment[a]	Area (mm^2) (mean ± SEM)
Smoke-exposed	17.81 ± 0.65
Sham-treated	16.30 ± 1.13
Control	14.20 ± 0.83
Sm. + Hal. 24 hr	18.57 ± 1.93
Sm. + Hal. 48 hr	17.88 ± 0.86
Sm. + Hal. 24 hr	17.52 ± 1.53
Sh. + Hal. 48 hr	17.97 ± 1.47
Cont. + Hal. 24 hr	14.51 ± 0.82
Cont. + Hal. 48 hr	14.74 ± 1.71

[a] Abbreviations: Sm., smoke-exposed; Hal., halothane anesthesia; Sh., sham-treated; Cont., control.

to determine the numbers PM and ARM. The sum of PM and ARM per unit area of lung tissue represents a certain relative fraction of the total (alveolar, septal, and airway) macrophage population.

Numerical data were evaluated statistically using Tukey's multiple comparison procedures (23). The statistical tests were carried out with an experimentwise error rate (overall significance level) of 0.05. Further, least squares regression procedures (23) was utilized to obtain the "best-fit" lines for the various animal groups in regard to percentages of macrophages noted in lung parenchyma and airways as a function of halothane effect over time.

Results

General Observations

The health of the animals during the experiment remained good. Animal body weights conformed to those recorded in earlier smoke exposure experiments (17) (Table 2). Deaths of animals during the 1-yr study were minimal (eight smoke-exposed, seven sham-treated, and two control) (Table 1) and were either attributed to natural causes or resulted from sacrificing animals that sustained injuries during loading or unloading into and out of the smoking or sham machines.

Anesthesia was achieved 15 min after the onset of halothane administration. Three smoke-exposed, two sham-treated, and one control animal died during the 2-hr halothane anesthesia. Sham-treated and control animals recovered significantly sooner from anesthesia ($P = 0.0001$; median test) (10 min) than the smoke-exposed mice (20 min).

Light and electron microscopic assessment of lung tissue revealed no pathology in any of the animals that could be attributed to anesthesia alone. However, smoke inhalation induced peribronchiolar and perivascular accumulations of lymphocytes and macrophages similar to those noted and discussed in an earlier report (17).

Degree of lung shrinkage or inflation, observed microscopically, appeared similar in animals subjected to different treatments. The areas of lung sections cut at the same location were likewise similar in all animals (Table 3) (α significance level 0.05).

Parenchymal Macrophage Morphology

Ultrastructure of PM in lungs of sham-treated and control animals was similar to that of sham-treated and control animals 24 and 48 hr after halothane inhalation. The macrophages appeared normal in the above-mentioned animal groups and were similar to phagocytes of normal mice described earlier (15). At both the light and electron microscopic levels, these cells were encountered infrequently in lungs of the above animals.

Macrophage ultrastructure of mice exposed to smoke only was likewise similar to that noted in smoke-exposed animals 24 and 48 hr after halothane treatment (Fig. 1); however, the morphology of macrophages in these animals differed markedly compared to that of phagocytes in control and sham-treated animals subjected or not subjected to halothane anesthesia. Phagocytes of the smoke-exposed mice appeared larger in size. Their cytoplasm was replete with heterogeneous, often large, secondary lysosomes (Fig. 1). In addition, many of these cells were characterized by

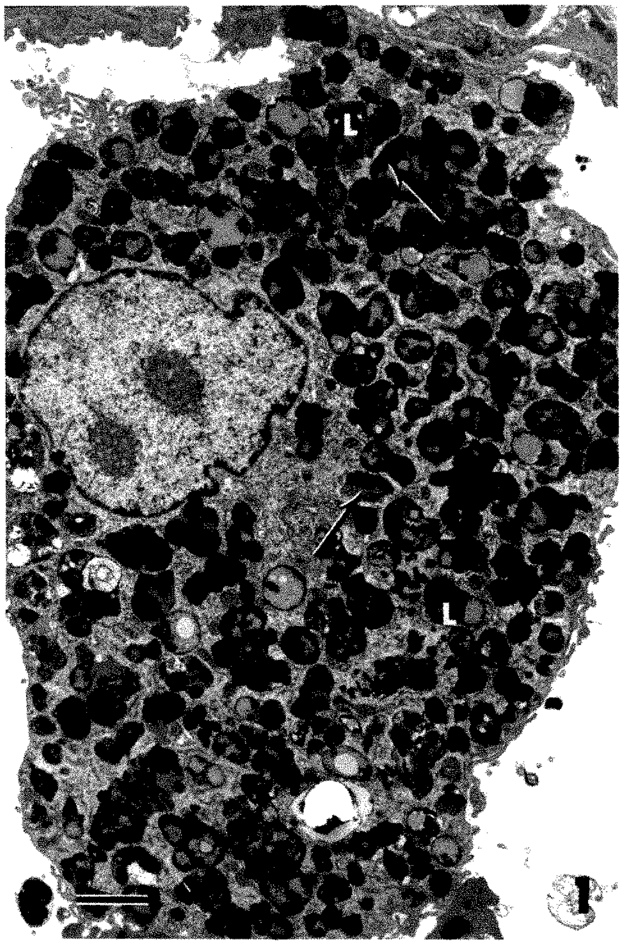

Figure 1. Electron micrograph of a parenchymal macrophage from a smoke-exposed animal 48 hr after halothane anesthesia. Many secondary lysosomes (L) are present in the cytoplasm, some containing needle-like inclusions (arrows). Calibration bar in the lower left corner equals 2 μm.

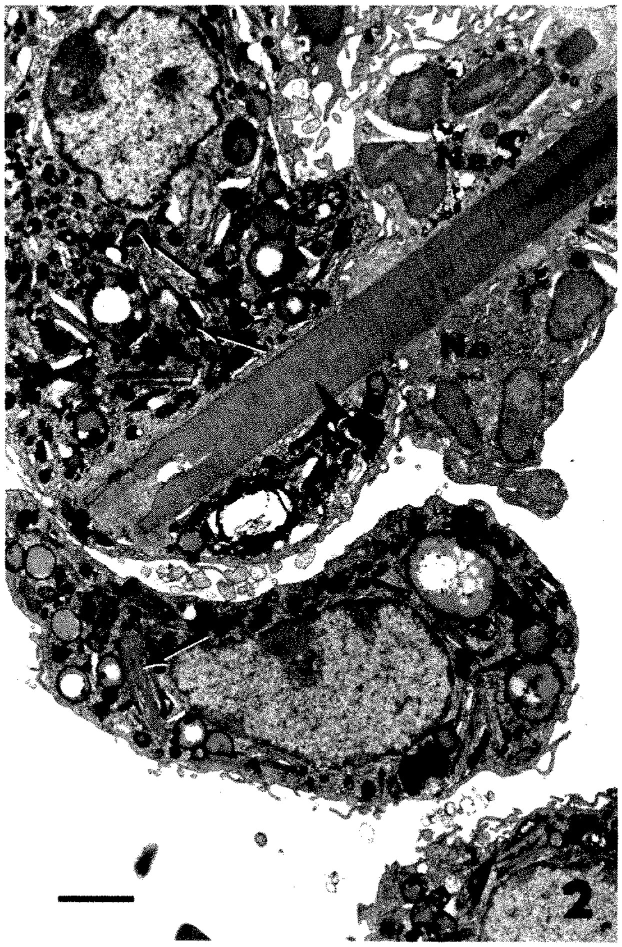

Figure 2. Electron micrograph of parenchymal macrophages from a smoke-exposed mouse 48 hr after halothane anesthesia. Note the numerous needle-like inclusions (arrows) associated with the lysosomes. An unusually large inclusion (arrowhead) appears to be partially engulfed by a macrophage and surrounded by several neutrophils (Ne). Calibration bar in the lower left corner equals 2 μm.

needle-, fiber-, or crystal-like inclusions that were associated with lysosomes or were free in the cytoplasm. These structures were only observed in smoke-exposed animal groups. Parenchymal macrophages were encountered frequently in the smoke-exposed only and in smoke-exposed mice 24 hr post halothane inhalation, but were often difficult to find in smoke-exposed animals 48 hr after anesthesia.

Airway Macrophage Morphology

The ultrastructure of ARM in the control, sham-treated, and smoke-exposed only and control and sham-treated animals 24 and 48 hr after halothane anesthesia was similar to that of PM of corresponding treatment groups with one exception, i.e., more lysosomes were noted in the cytoplasm of most of the former cells. ARM in lungs of smoke-exposed animals were similar in morphology 24 and 48 hr after halothane anesthesia but differed considerably from those noted in the above groups. The cytoplasm of many, though not all ARM, was replete with the fiber- or crystal-like inclusions (Fig. 2) morphologically similar to those noted in parenchymal macrophages of smoke-exposed mice. Often the inclusions were quite large and appeared to be encased by several macrophages or phagocytes and neutrophils (Fig. 2) suggesting an extracellular position. These structures were only seen in smoke-exposed animal groups.

Airway macrophages were rarely encountered, even at the light microscopic level and much less in the electron microscope, in lungs of sham-treated and control animals (not observed in four of the ten animals). However, occasionally a visual field of airways in lungs of smoke-exposed mice contained as many as three macrophages (Fig. 3**a**). Similar numbers were

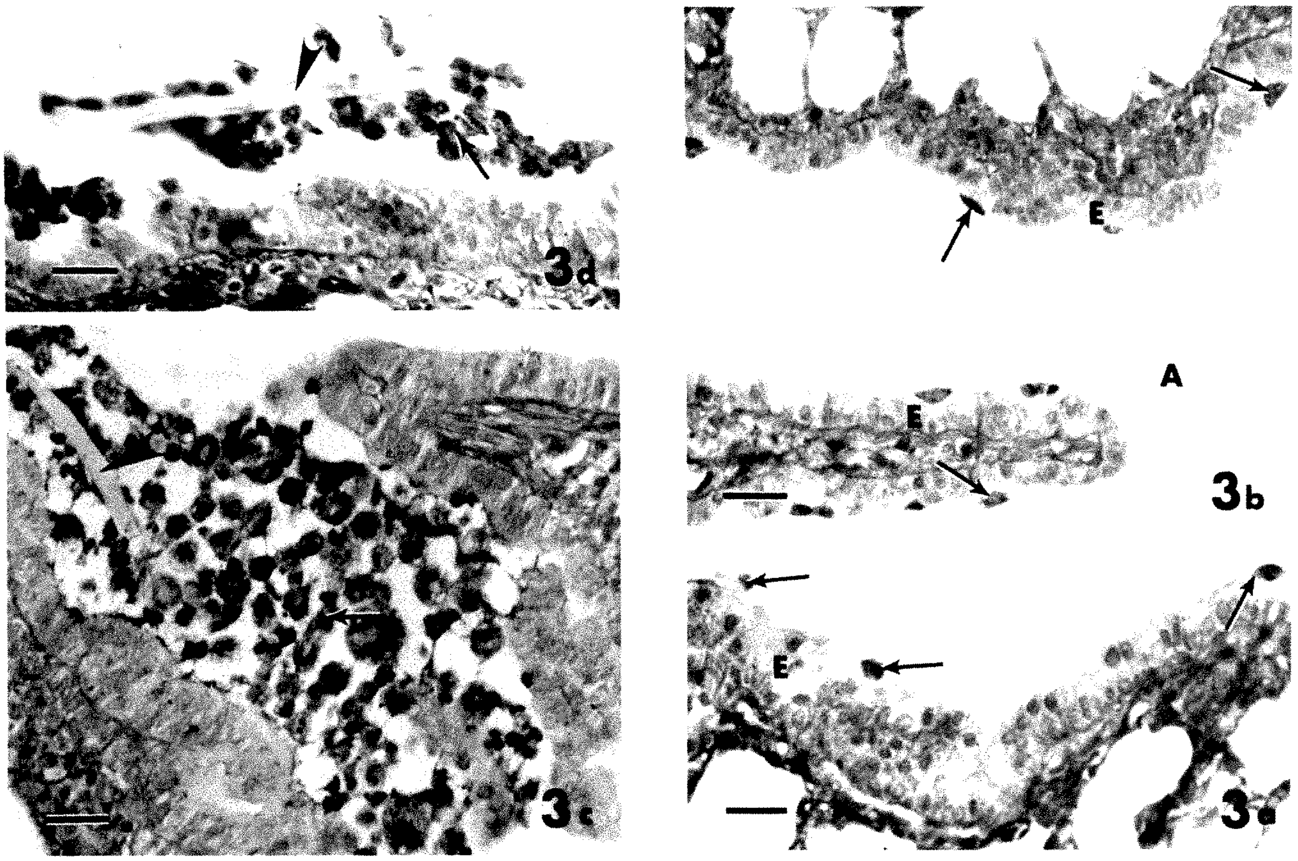

Figure 3. (**a**) Light micrograph of a small airway from a smoke-exposed animal showing three macrophages (arrows) attached to the epithelium (E). This and subsequent light micrographs were obtained from sections stained with periodic acid Schiff reagent-hematoxylin. Calibration bar in the lower left corner of this and all other light micrographs equals 20 μm. (**b**) Light micrograph of airways (A) from a smoke-exposed mouse 48 hr after halothane anesthesia showing numerous macrophages (arrows) uniformly distributed over the epithelium (E). (**c**) Light micrograph of an airway from a smoke-exposed animal 24 hr after halothane anesthesia showing a large aggregation of macrophages (arrow) that appears to occlude the airway. Note the large fiber needle-like inclusion (arrowhead) surrounded by macrophages. (**d**) Light micrograph of a larger airway from a smoke-exposed animal 48 hr after halothane anesthesia depicting an aggregation of macrophages (arrow), which surround a fiber-like inclusion (arrowhead).

observed in sham-treated and control mice 24 and 48 hr after halothane inhalation. In contrast, airways of smoke-exposed mice examined 24 and 48 hr after anesthesia had numerous phagocytic cells (Fig. 3**b**–**d**). In some airways of the smoke-exposed animals 24 and 48 hr after halothane anesthesia, the distribution of these cells was relatively uniform (Fig. 3**b**) while in others they were aggregated in groups of 50 or more (Fig. 3**c**). On occasion, long needle- or fiber-like structures were noted in such aggregations of macrophages (Fig. 3**c**,**d**).

Morphology of Airway Epithelium

With the exception of ciliated cells in smoke-exposed animals 24 and 48 hr after halothane inhalation (Fig. 4**a**), the ultrastructure of all other cellular components appeared normal (Fig. 4**b**) in the different groups of animals. In longitudinal sections of airway epithelium, many (though not all) of the ciliated cells in airways of the two affected animal groups were characterized by reduced numbers of cilia (Fig. 4**a**). Those that were present were short in stature. Basal bodies were disoriented, some of which were randomly distributed in the supranuclear cytoplasm at some distance below the surface of the cell (Fig. 4**a**). Precursor material of ciliary basal bodies was observed near the cell surface (Fig. 4**a**).

Quantification of Parenchymal and Airway Macrophages

Quantification of macrophages in the lungs of the different animal groups revealed that different treatments or combinations of treatments altered the PM, ARM, and total macrophage population size (Fig. 5). PM population size of all control and sham-treated

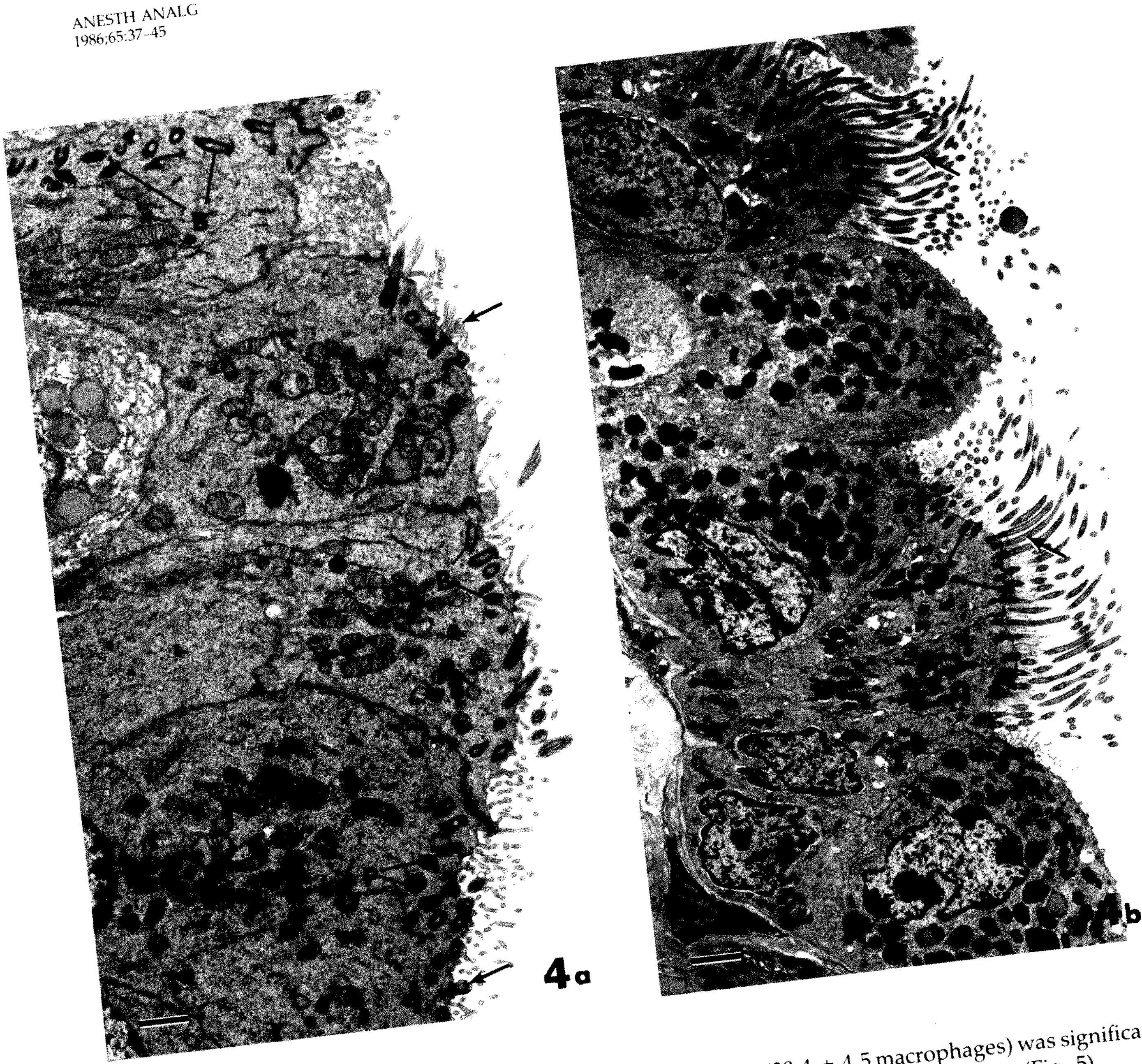

Figure 4. (a) Electron micrograph of the apical portion of airway epithelium from a smoke-exposed mouse 48 hr after halothane anesthesia showing abnormal appearing cilia (arrows). Basal bodies (B), basal body precursor material (P). The calibration bar in the lower left corner equals 1 μm. (b) Electron micrograph of normal airway epithelium from a sham animal 48 hr after halothane. Cilia (arrows), basal bodies (B). The calibration bar in the lower left corner equals 2 μm.

groups was similar (Fig. 5). The number of these cells in smoke-exposed mice 48 hr after anesthesia administration (14.7 ± 1.4 macrophages) was the same as that noted in sham-treated (10.3 ± 2.6 macrophages) and control (6.2 ± 0.3 macrophages) animals 24 hr after halothane anesthesia (Fig. 5). PM population in mice exposed to smoke only (32.3 ± 2.0 macrophages) and in smoke-exposed animals 24 hr after halothane anesthesia (30.4 ± 4.5 macrophages) was significantly greater than in other animal groups (Fig. 5).

In regard to the airway macrophage population size, a significant increase (46.8 ± 15.6 macrophages) over all other groups (0.0–17.0 ± 3.1 macrophages-range) was noted only in smoke-exposed animals 48 hr after halothane (Fig. 5). The number of macrophages in airways of smoke-exposed mice 24 hr after anesthesia (17.0 ± 3.1 macrophages) was likewise significantly greater than that noted in smoke-exposed only (0.8 ± 0.4) and all sham-treated and control groups (Fig. 5). Quantitative procedures were not sensitive enough to detect the few ARM noted in airways of sham-treated and control mice during morphologic assessment.

The total macrophage population size (PM plus

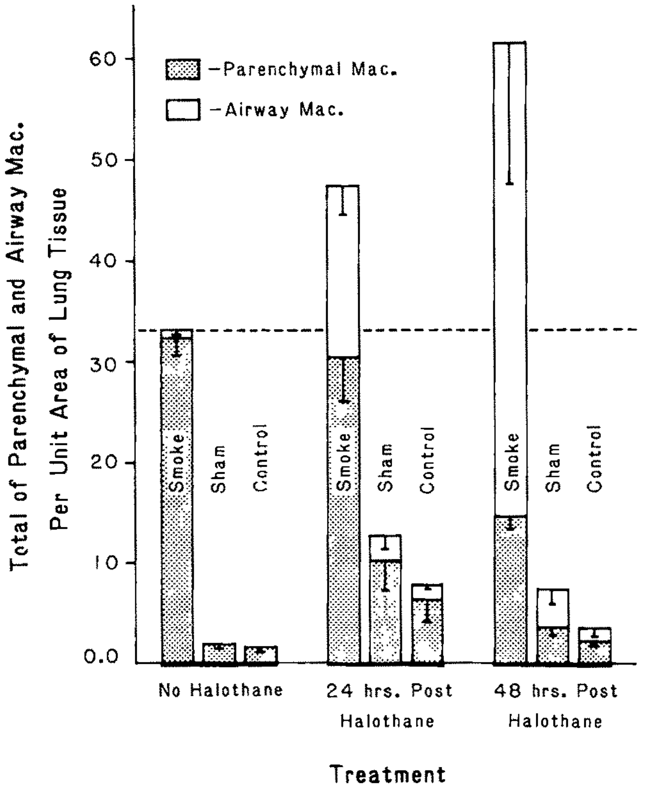

Figure 5. The total number of parenchymal and airway macrophages (Mac.) per unit area of lung tissue over different treatments. The shaded portion of the bars represents parenchymal macrophage population while the clear portion represents that of airway phagocytes. Number of parenchymal macrophages is significantly larger ($P < 0.05$) in the smoke only mice and smoke-exposed animals 24 hr after halothane anesthesia and that of airway phagocytes of smoke-exposed animals 24 and 48 hr after anesthesia than all other values. Vertical lines denote one standard error of the mean. The horizontal broken line represents the total lung macrophage population size of smoke-exposed animals.

ARM) in the three smoke-exposed groups of animals was significantly greater than in sham-treated and control groups (Fig. 5). Further, the number of these cells was significantly greater in smoke-exposed animals 48 hr after anesthesia than in smoke-exposed only animals. The total number of macrophages was the same in all control and sham-treated animals (Fig. 5). The percent of ARM evaluated, using least square regression analysis, in the smoke groups showed the greatest trend to increase with time after halothane anesthesia (Fig. 6). Likewise, ARM percent in the sham groups treated with the anesthetic was elevated over time, though more modestly than in the smoke groups (Fig. 6). The percent of these cells was least affected by the anesthesia treatment in control groups (Fig. 6). The percentages of parenchymal macrophages were affected by halothane anesthesia over time exactly as those of the ARM except in the opposite direction, i.e., decreases rather than increases occurred.

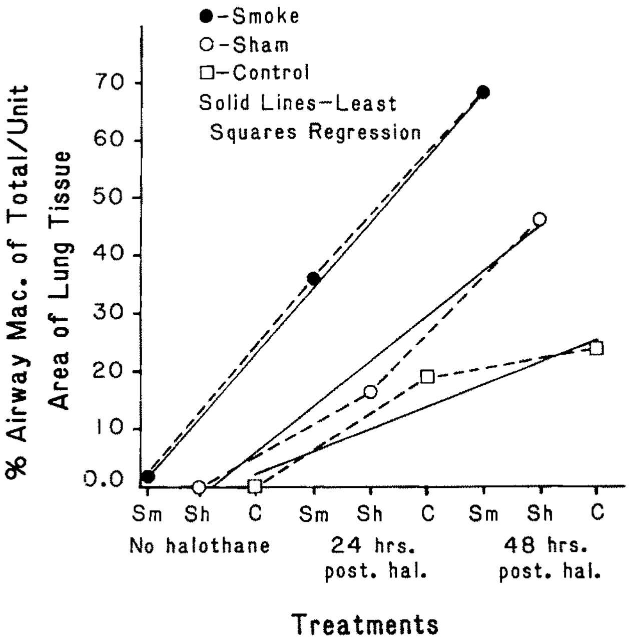

Figure 6. Percent of airway macrophages (Mac.) of the total macrophages (parenchymal plus airway) per unit area of lung tissue over different treatments (broken lines) and least squares regression analysis (solid lines). Note that the percent of airway macrophages is highest in the smoke exposed mice 48 hr after halothane anesthesia. Halothane (hal).

Discussion

Even though no general lung morphologic alterations attributable to halothane were noted, the present study revealed that halothane induced macrophage ultrastructure and population size changes. Parenchymal macrophage morphology in lungs of mice exposed to smoke or to smoke and halothane was similar but differed markedly when compared with sham-treated and control animals. Phagocytes in the former animal groups appeared larger and contained considerably more heterogeneous, often large, secondary lysosomes. Many of these organelles had embedded within them needle-, fiber-, or crystal-like inclusions. In general, the size and morphology of PM were similar to those described previously after 24 weeks of smoke exposure (15). Increase in macrophage size and accumulation of lysosomal bodies reflect increased demand for smoke particulate phagocytosis or intracellular digestion of such material (13,24,25). Halothane did not appear to influence PM size or lysosomal morphology.

Airway macrophage morphology in lungs of animals exposed to smoke and anesthetized by halothane differed in structure from PM. The ARMs were characterized by more fiber- or crystal-like inclusions when compared to PMs. The presence of ARMs with such a burden of material cannot be explained at present. However, these cells may represent effete phagocytes that have endocytosed maximal quantities of undigestable material (the crystalline-like material) and are being cleared from the lungs.

Total number of lung macrophages (PM plus ARM) was most markedly elevated in the smoke-exposed animals 48 hr after anesthesia. The specific mechanism that induces the increase in the macrophage population in smoke-exposed animals subsequent to halothane anesthesia cannot be accounted for presently. However, the data suggest that halothane is involved in the observed phenomenon. It is possible that macrophages or other lung cells are stimulated by the anesthetic to liberate substances that are chemotactic for phagocytes. Such a notion has been proposed in regard to the mechanism that normally causes the lung macrophage population to increase in response to smoke inhalation (16,26,27).

While total number of pulmonary phagocytes increased, the population of PM decreased after halothane anesthesia in the smoke-exposed animals 48 hr after anesthesia. It is possible that the majority of the lost PMs appeared as ARMs because the population of the latter increased after halothane exposure, especially in smoke-exposed animals. As noted previously, the ARM might represent, at least in part, an effete PM population whose phagocytic role has been completed, which is being cleared from the lungs passively. On the other hand, active mobilization of PM into airways may be the result of increased demand for airway clearance, particularly of accumulated mucus, after the anesthetic exposure. Postanesthetic impairment in mucus transport is known to occur in humans (28) and dogs (29).

The decrease in PM population could reflect a decrease in the antibacterial defenses of the lungs in the postanesthetic period because such defenses of the lungs are known to be dependent primarily on PM function (30). Cigarette smoking increases the risk of pulmonary complication after anesthesia, including the inability to clear mucus as well as increased vulnerability to bacterial infection (2). Morphologic observations suggesting that cilia of airways sustained more damage in smoke-exposed animals that were also exposed to halothane support the notion that smoking and anesthesia could be associated with derangement of the mucociliary escalator system (5,28 31). It seems possible that halothane anesthesia participates additively to smoke inhalation in regard to impairing clearance of material from the lungs, which causes accumulation of the phagocytes in the airways. These cells might add to congestion in the passageways that initially results from mucus accumulation. It is conceivable that the added airway burden is sufficient to impede airflow into alveolar regions, which may contribute, in part, to the postanesthetic pulmonary complications observed in humans.

It is acknowledged that the above speculations are based on morphologic data and that dynamic assessment of ciliary function and macrophage mobilization is necessary before mechanisms for the observed cellular responses can be proposed. Secondary effects induced during anesthesia, e.g., respiratory depression and hypoventilation (32–35) might also contribute to eliciting the responses. Further animal research designed to specifically delineate the relationship of smoking, macrophage dynamics, and secondary effects of anesthesia to lung pathophysiology is indicated. Such studies may yield important, clinically relevant information.

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Myocardial Metabolism and Hemodynamic Responses with Fentanyl–Enflurane Anesthesia for Coronary Arterial Surgery

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MOFFITT EA, McINTYRE AJ, BARKER RA, IMRIE DD, MURPHY DA, LANDYMORE RW, KINLEY CE. Myocardial metabolism and hemodynamic responses with fentanyl–enflurane anesthesia for coronary arterial surgery. Anesth Analg 1986;65:46–52.

Ten patients for coronary vein grafting had induction of anesthesia with fentanyl (30 μg/kg), followed by enflurane–oxygen sufficient to decrease systolic blood pressure by 27% before intubation. Enflurane was continued in concentrations to maintain blood pressure below that with patients awake. All patients had preserved ventricular function and effective β-blockade. Studies of hemodynamic functions and myocardial blood flow and oxygenation were done before induction, six times during anesthesia, and twice postoperatively. The blood pressure decrease on induction and before bypass was due to reduced cardiac index without decreased heart rate or systemic resistance. Stroke work index decreased 47% on induction and remained below awake level throughout. Coronary sinus blood flow decreased 26% after intubation and remained so before bypass. Without change in coronary resistance, coronary sinus oxygen content increased 30% on induction and stayed elevated before bypass. Normal lactate extraction continued after induction and increased before bypass; mean extraction decreased after bypass, with one or two hearts producing lactate in the first 24 postoperative hr. Fentanyl–enflurane–oxygen maintained a steady mild hemodynamic depression during the operation and soon afterward, which preserved myocardial oxygenation.

Key Words: ANESTHETICS, VOLATILE—enflurane. ANESTHETICS, INTRAVENOUS—fentanyl. SURGERY, CARDIOVASCULAR.

The principle that to preserve myocardial oxygen balance during anesthesia in patients with coronary disease, factors responsible for oxygen consumption must be controlled closely (1) has become widely accepted. Heart rate and blood pressure cannot be allowed to increase significantly over quiet awake levels. Several studies have shown that fentanyl, even in high doses, does not assure a hypodynamic circulation (2,3), thus risking myocardial ischemia (4,5). Although enflurane with oxygen can be given to consistently depress the heart and circulation during cardiac surgery (6), early waking occurs with the risks of hypertension. A moderate dose of intravenous fentanyl, followed by controlled circulatory depression with a potent inhaled agent, has become a popular treatment because of a clinical impression of its effectiveness. We studied 10 patients before, during, and after fentanyl-plus-enflurane anesthesia for coronary artery bypass grafting (CABG). Effects on hemodynamics and cardiac performance were correlated with coronary blood flow, myocardial oxygen consumption (MV_{O_2}), and lactate extraction (MLE).

Methods

Patient Population

Ten men gave informed signed consent for the study. Mean age was 60.8 yr (range 53–67) and mean weight 81.4 kg (range 67–100). All were typical CABG candidates with preserved ventricular function: seven had areas of hypokinetic muscle but nine had normal heart size; only three had known previous infarction. At cardiac catheterization, mean cardiac index was 2.49 $L\cdot min^{-1}\cdot m^{-2}$ (range 1.92–3.23), mean left ventricular end diastolic pressure (LVEDP) 10 mm Hg (range 6–13), and mean ejection fraction 0.73, with none under 0.50. All patients were normotensive preoperatively. NYHA

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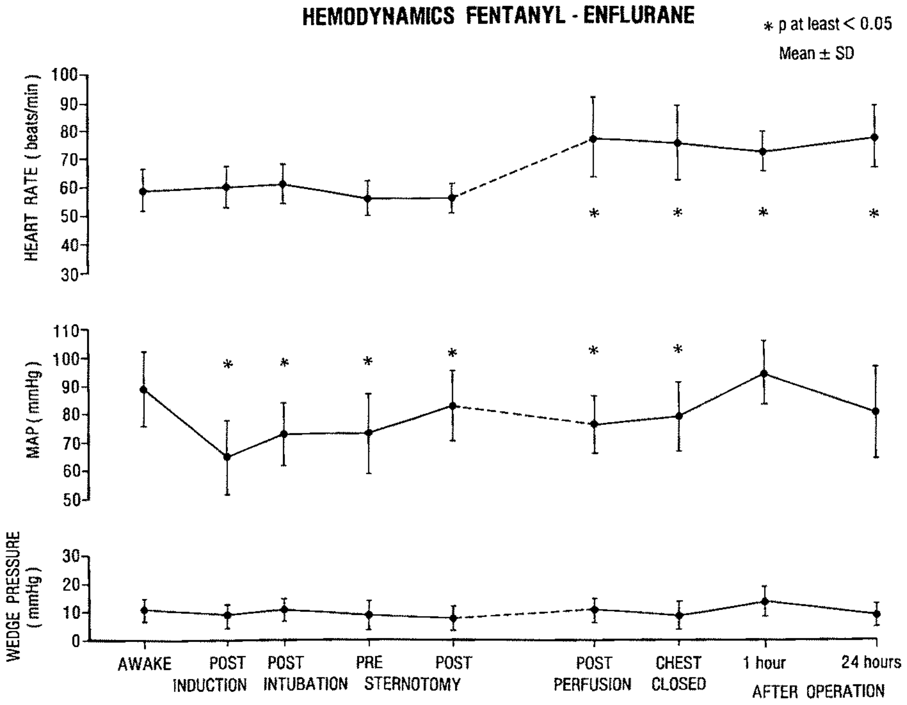

Figure 1. Mean ± SD for heart rate, mean arterial and wedge pressures in 10 patients through operation and postoperatively. The significant decrease in MAP below awake values continued through anesthesia.

disability was class II in one, III in seven, and IV in two patients. Surgery included insertion of a mean of 2.5 vein grafts (range 1–4). All ten patients were maintained on effective doses of β-blocking drugs until the operation; two were also taking a diuretic, one digoxin, and two an oral hypoglycemic drug for diabetes.

Study Protocol

The study, approved by our institutional Ethics Committee, included premedication with diazepam, mean 10.5 mg (range 10–15) and morphine, mean 13 mg (range 10–15), followed by insertion of intravenous and radial arterial cannulae under local anesthesia. To increase drowsiness, additional intravenous diazepam (mean 5.7 mg, range 2.5–10) was given. Two thermodilution catheters were then inserted through the right internal jugular vein: one into the pulmonary artery (PA) (7), the other, a Ganz catheter (8), into the midcoronary sinus, aided by fluoroscopy and injection of contrast medium. The latter measured total coronary sinus blood flow (CBF), essentially left coronary arterial inflow.

Lead V5 of the ECG was monitored continuously. Nine sequential studies were done starting before induction of anesthesia and continuing through anesthesia and into the postoperative period. Each study recorded measurements of cardiac output (duplicate), CBF, ECG, and arterial and central pressures. Arterial and coronary sinus (CS) blood was drawn for measurement of oxygen saturation and hemoglobin (co-oximetry) and lactate content (Boehringer Mannheim, Canada, Ltd.). Oxygen content was calculated from oxygen saturation × hemoglobin × 1.34. From measured data, MVO_2 was calculated as the product of CBF times the arterio–CS difference of oxygen content and MLE as that portion of arterial lactate extracted by muscle, i.e., arterio–CS lactate difference × 100 divided by arterial lactate content. If more lactate is in CS than in arterial blood, lactate has been produced by myocardial anaerobic glycolysis. Statistics included analysis of variance and paired *t*-tests with $P < 0.05$ considered to be significant.

Anesthetic Protocol

Induction began with 30 μg/kg of intravenous fentanyl, mean dose 2450 μg (range 2000–3000), given over 2 min. Pancuronium, mean dose 8.4 mg (range 7–10), was given slowly during the fentanyl administration. Enflurane was then added to the inspired oxygen to reduce systolic arterial pressure 25–30% from the awake levels and to maintain it there for a total induction time, averaging 10.2 min (range 8–12) before the second study. End-expiratory concentration of enflurane averaged 1.62% (range 0.75–2.2) over this period. After intubation, enflurane–oxygen was continued to maintain a steady, slight decrease in arterial pressure using concentrations of enflurane that varied up to 3%. No intravenous fluid was given during induction, other than that given as a vehicle for drugs, but thereafter the usual amounts of fluid and

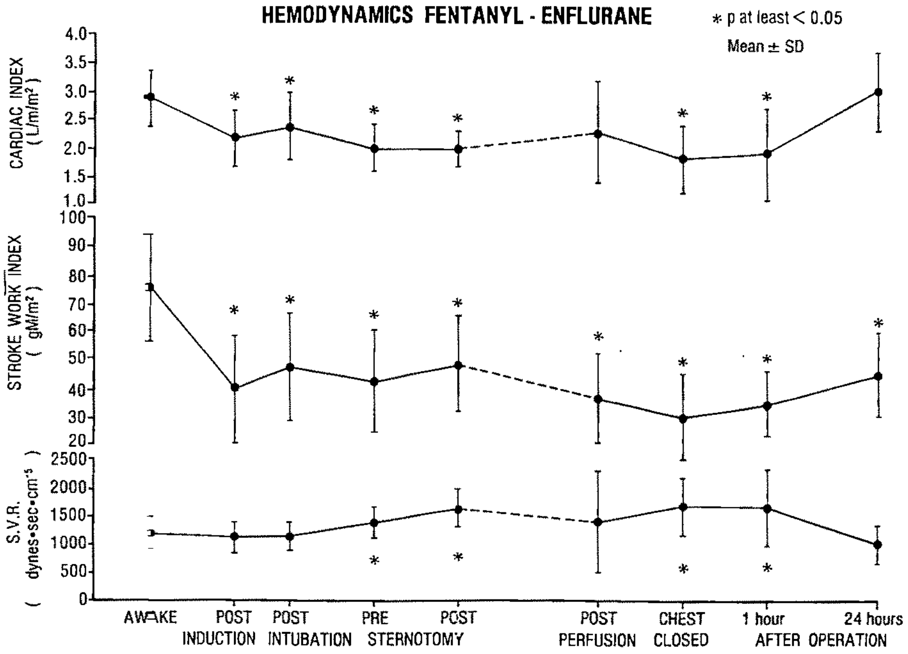

Figure 2. Cardiac index decreased on induction and remained so throughout anesthesia. Stroke work index likewise was reduced throughout. Systemic resistance increased at sternotomy and at the end of anesthesia.

blood products were administered throughout bypass, operation and afterwards. No further fentanyl was given. Postoperatively, sedation and analgesia were with intravenous diazepam (2.5-mg doses) and pantopon (3-mg doses) through the 24-hr final study.

Results

Induction was smooth in all cases, with no episodes of tachycardia or hypertension. Mean Pa_{CO_2} when awake was 40 mm Hg; after induction it was 45 mm Hg. Duration of anesthesia averaged 255 min (range 194–409); cardiopulmonary bypass (at 26°C) lasted 95 min (range 50–165) with an average aortic cross-clamp time of 36 min (range 16–63). Other than $CaCl_2$ on discontinuing bypass, no cardioactive drugs were needed except nitroglycerin infusion during rewarming to control blood pressure in one patient and a dopamine infusion for a short period after bypass in another patient. After the study at 1 hr, two patients received nitroprusside for hypertension. The time to first response to command postoperatively averaged 92 min (range 30–195) with the time to extubation 13.5 hr (range 5.5–19). No patients had evidence of infarction postoperatively; all were discharged in 7–10 days without major complications.

Mean heart rate was 59 beats/min before induction and did not change until after bypass (Fig. 1). Mean arterial pressure (MAP) was intentionally lowered (mean, 27%) during induction; it was still 18% below awake levels after intubation. Throughout anesthesia MAP was kept 10–20% below awake levels; at 1 hr postoperatively it had risen only to the preinduction value. Pulmonary capillary wedge pressure remained unchanged throughout the study. Blood pressure control was achieved by decreases in cardiac index (CI): 24% on induction and 30% before and after sternotomy (Fig. 2). Cardiac index was also reduced after chest closure and at 1 hr postoperatively, but by the next day had fully returned to the preoperative state. With decreases in MAP and CI, stroke work index remained 25–47% below the preinduction level. Systemic vascular resistance (SVR) did not change on induction or intubation but increased before sternotomy. Mean SVR increased to 1690 dynes-sec-cm^{-5} after chest closure and 1667 at 1 hr; by the next morning it had returned to normal.

Mean CBF in the quiet awake state was 113 ± 30.9 ml/min (Fig. 3). The decrease (26%) present after intubation became greater (48%) after sternotomy. After bypass mean CBF was at preinduction level and was higher at the 24-hr study than preinduction. Coronary vascular resistance (CVR) did not change except for an increase after sternotomy at a time when CBF was at its lowest point.

Oxygen content of CS blood (CS_{O_2}) increased 30% on induction because of an FI_{O_2} of 1.0, and a decrease in cardiac work (Fig. 4). This elevated content lasted until bypass. After bypass CS_{O_2} gradually increased as hemoglobin levels increased, until at 24 hr it was 23% greater than before induction. $M\dot{V}_{O_2}$ decreased 24% on induction and remained below awake level until bypass. $M\dot{V}_{O_2}$ did not reach awake levels until 24 hr postoperatively.

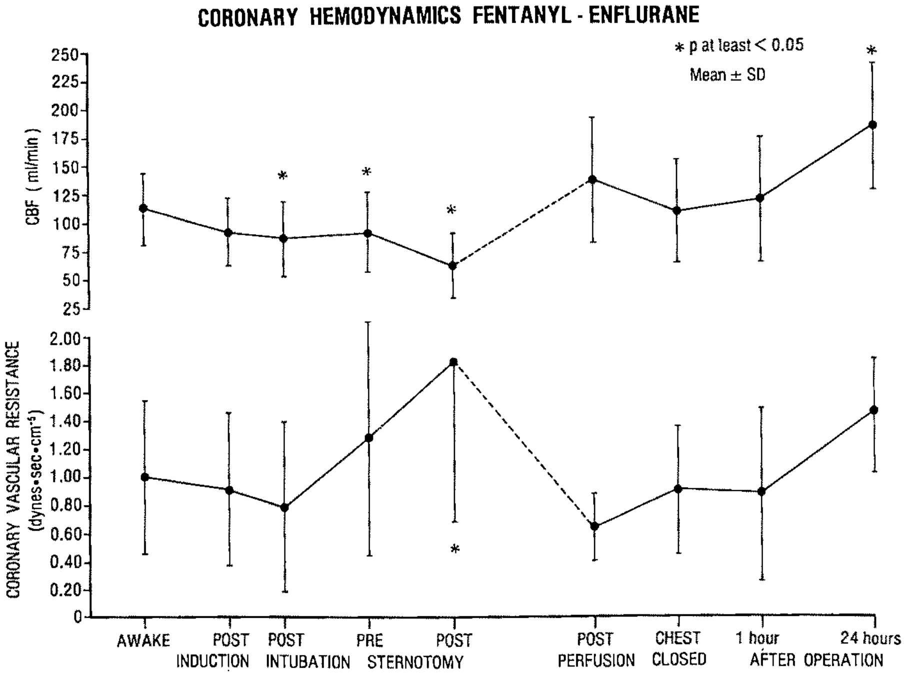

Figure 3. Mean coronary blood flow was below awake level from intubation until bypass. Coronary vascular resistance changed only after sternotomy, when CBF was lowest.

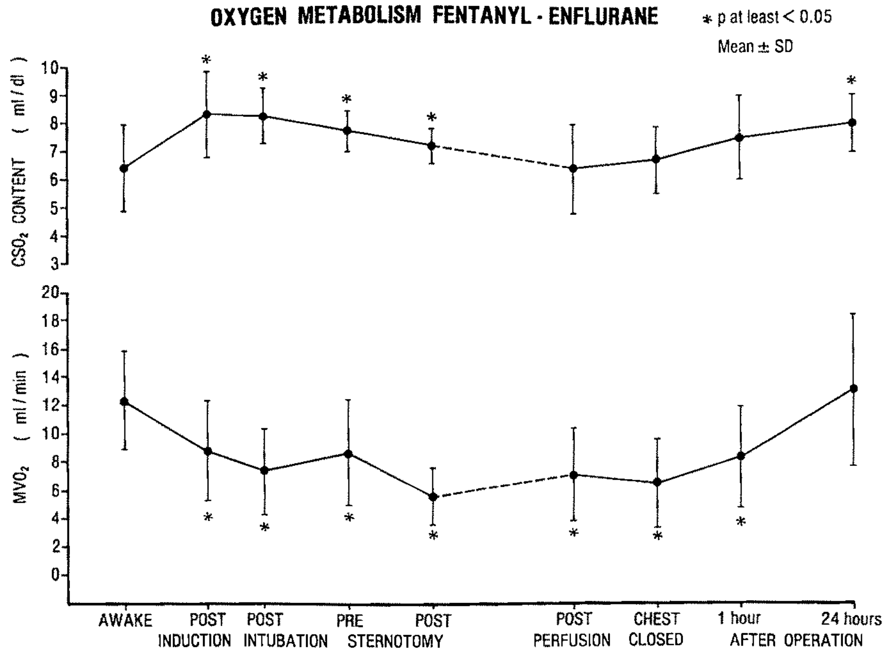

Figure 4. Coronary venous oxygen content increased on induction and continued elevated until bypass. Myocardial oxygen consumption was below awake level throughout anesthesia.

Arterial and CS contents of lactate increased before sternotomy; after bypass both reached three times preoperative levels and had not yet returned to normal value at 24 hr (Fig. 5). Mean MLE did not change until it increased after sternotomy. One patient had myocardial lactate production after induction. Myocardial lactate extraction was lower than awake at all study times after bypass, with production seen in one patient after chest closure, in one at the 1-hr and in two at the 24-hr periods. ST segment depression of 2 and 1 mm, present in two patients before induction, decreased to 1 mm and 0 after intubation. Another patient had 2 mm of ST segment depression when awake, which did not change before sternotomy; postbypass ST elevation was present. Six other patients developed 1–2 mm of ST segment elevation

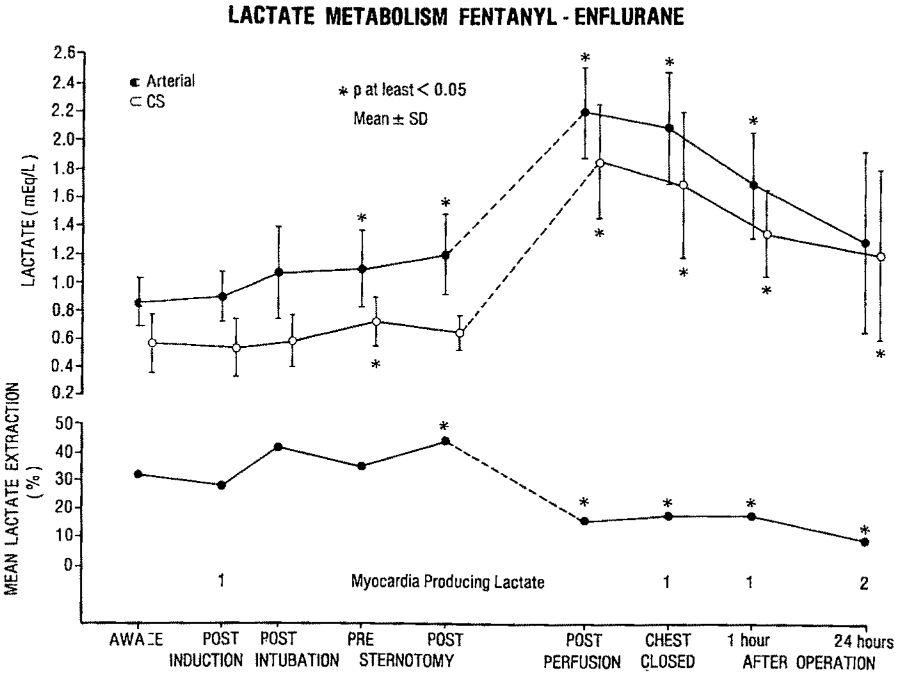

Figure 5. Arterial and CS lactate levels increased before bypass and were much higher after bypass. Mean lactate extraction after bypass was consistently below that before bypass.

from the postinduction through poststernotomy studies.

Discussion

The first reports of effects of anesthetics on coronary blood flow and myocardial oxygenation in humans with coronary disease began in 1979. Methods included arterial–CS venous argon differences by Sonntag et al. (9) and measurement of arterial–CS venous oxygen content differences and coronary sinus blood flow by Wilkinson (10). With the continued work of Sonntag et al. (4,9,11,12), along with that of Reiz et al. (13–16) and our multiple studies (5,6,17–20), the major agents in common use for cardiac anesthesia have been investigated.

These reports have proven the maxim that myocardial oxygen balance during anesthesia in patients with coronary arterial disease is preserved by controlling the factors governing MV_{O_2}. Heart rate and blood pressure must be kept at normal levels or below. Both halothane (17) and enflurane (6), given alone for CABG operations, can maintain the appropriate hemodynamic depression. Fentanyl, even in high doses, does not, however, always retain a hypodynamic circulation (4,5). Nitrous oxide may contribute to insidious ischemia distal to areas of coronary stenosis (19,20). Isoflurane is a potent coronary vasodilator (15,18), but may cause coronary "steal" detrimental to oxygenation in regions of reduced blood flow. From their clinical experience, cardiac anesthesiologists now frequently combine anesthetic drugs, using each for specific properties to provide the necessary range of effects. The present report validates that approach, showing that with fentanyl for basic analgesia and enflurane as needed for obtunding autonomic reflexes, oxygen balance is preserved. All our patients had good ventricular function with no other serious lesions, but these patients are more likely to develop a hyperdynamic circulation than those with class IV disability. If this combination fulfills the need in the patient with a robust myocardium, its careful application should be appropriate for the more severely disabled heart, with the opiate and inhaled agent given to fit their lesser tolerance.

Quantitation of Myocardial Oxygenation

We have continued measurements of coronary flow by thermodilution because it accurately determines total flow through left ventricular muscle over a 20-sec period and can be repeated in 1–2 min. While not detecting moment-to-moment changes that occur in regional flow (21), the rapid response time does document alterations in global flow due to major events as induction, intubation, and sternotomy. Mean flow is measured for the whole ventricle; variations in flow distal to coronary lesions cannot be identified. Similarly, measurement of energy substrates and metabolites in coronary venous blood quantitates only global oxygenation. Only when most of the ventricular muscle becomes ischemic can anaerobic glycolysis be identified by finding more lactate in coronary venous than in arterial blood.

Hemodynamic Responses

Our patients, all kept on full doses of β-blocking drugs, then heavily premedicated and given 30 μg/kg of fentanyl, had no increases in heart rate associated with pancuronium (0.1 mg/kg) or intubation. None had increased ST segment depression, as found by Thomson and Putnins (22). The increase in heart rate normally seen after bypass was, however, still present. Little reduction in blood pressure occurred with fentanyl alone, so enflurane was added to intentionally decrease blood pressure and to keep it below control levels. After a 10-min induction, the second study reflected responses to the two agents without a change in blood gas tensions. From that base, intubation produced no hyperdynamic response. Subsequently, blood pressure was controlled below awake levels by using enflurane to decrease cardiac index, with systemic resistance actually increasing slightly before bypass. This anesthetic depression of myocardial pumping function was not sufficient to increase either left or right atrial filling pressure. By using enflurane, hemodynamic response to sternotomy was eliminated. In contrast to use of inhaled anesthetics alone, (6,17,18), mean blood pressure for the group increased only to normal at 1 hr postoperatively. Two patients needed vasodilator therapy in the early postoperative hours, compared to nearly all those after anesthesia with inhaled agents given alone. Fentanyl provided effective postoperative analgesia.

Myocardial Oxygenation

The initial major decrease in cardiac work continued throughout surgery and anesthesia as heart rate, blood pressure, and cardiac output remained constant. Hence on induction, oxygen content of coronary venous blood increased 30% and remained elevated until bypass. Thus, calculated left ventricular $M\dot{V}O_2$ decreased and remained so throughout anesthesia. With greatly diminished cardiac work, less oxygen was needed by the myocardium and globally less was extracted from the coronary circulation, but no conclusions on regional supply are possible.

An indication of oxygenation can be obtained from examining lactate exchange across the myocardium. Normally, lactate is extracted in proportion to its arterial concentration (21): MLE tended to increase with increase in arterial lactate content before bypass. After bypass, myocardial lactate extraction remained below the 32% awake level in spite of a much elevated arterial content. Either cellular uptake was diminished or the cells were producing more lactate, which appeared in CS blood. More lactate was present in CS than in arterial blood in one patient after chest closure, in another patient at 1 hr, and in two patients at 24 hr. No ECG or other evidence of ischemia was observed in these patients, and this greater amount of lactate in CS blood may have been due to lactate formed during cold cardioplegic arrest. Oxygen balance was preserved before bypass, as evidenced from only one instance of lactate production (after induction) in all ten patients at the four study periods.

This study of fentanyl–enflurane–oxygen and our previous study of enflurane–oxygen (6) both documented preservation of myocardial oxygenation during steady, mild hemodynamic depression. Rydvall et al. (16), however, have reported that enflurane–nitrogen–oxygen anesthesia has potent coronary vasodilating effects and hence may induce myocardial ischemia. Several real differences in their protocol from ours seem sufficient to account for the opposite findings and conclusions. First is that almost all of their patients were taking neither β- nor calcium-blocking drugs, compared to full β-blockade in ours. They probably produced a deeper anesthetic state: "A stable end-tidal concentration of 1.4%" for "approximately 30 minutes after intubation" before their second study. Our second study was after 10 min and before intubation. Deeper anesthesia is shown by their 50% decrease in mean arterial pressure (27% in ours) and 41% decrease in systemic resistance (ours, no change). Another real difference between the studies was that their $F_{I_{O_2}}$ throughout was 0.3 with 70% nitrogen, while we gave only oxygen. They showed that enflurane can be a potent peripheral and coronary dilator and produce myocardial ischemia, if enough is given. Our studies showed that enflurane–oxygen and moderate dose fentanyl plus enflurane can achieve mild but steady hemodynamic depression and effectively avoid ischemia.

Coronary Blood Flow and Resistance

Left coronary flow in these awake, sedated patients averaged 113 ± 31 ml/min, levels we regularly find at that time in similar studies (5,6,17,18). Coronary flow varied considerably from patient to patient, but in general correlated with blood pressure. Because of the wide standard deviation in coronary blood flow measurements, the decrease to 91 ml/min after induction was not statistically significant. After the period of cardioplegia and with the bypass grafts, CBF immediately after bypass was back to awake levels; next morning it was higher than preoperatively. We saw no change in total coronary vascular resistance with induction, which has been our usual finding except for the reduction observed with isoflurane (18). As a calculation depending largely on CBF, CVR was significantly elevated after sternotomy, when CBF was lowest. This measure of coronary resistance is also a mean for the whole bed that reveals nothing about resistance in the local vascular beds distal to coronary lesions.

In summary, the combination of fentanyl induction (30 μg/kg), followed by enflurane–oxygen titrated to maintain mild hemodynamic depression, resulted in a steady hypodynamic state in CABG patients with good ventricular function. Myocardial oxygenation before bypass was preserved, as indicated by elevated coronary venous oxygen content and continued myocardial lactate extraction.

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Myocardial Metabolism and Hemodynamic Responses with Isoflurane Anesthesia for Coronary Arterial Surgery

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MOFFITT EA, BARKER RA, GLENN JJ, IMRIE DD, DELCAMPO C, LANDYMORE RW, KINLEY CE, MURPHY DA. Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary arterial surgery. Anesth Analg 1986;65:53–61.

Isoflurane–oxygen was given for induction and maintenance of anesthesia to ten patients having coronary artery bypass grafts. All had preserved ventricular function without hypertension or other cardiac lesions; treatment with β-blocking drugs was maintained until the operation in all patients. Cardiac output, arterial and central pressures, coronary sinus (CS) blood flow, arterial and CS oxygen, Hb, and lactate contents were measured before, six times during, and twice after anesthesia. On induction, systolic arterial pressure was purposely reduced 33% along with systemic resistance by increasing the concentration of isoflurane; cardiac index, heart rate, and coronary flow did not change. Coronary resistance decreased 23% and CS oxygen content increased 56%; but in three of ten patients myocardial lactate production took place, evidence of global ischemia. Induction of anesthesia was not smooth in three patients. Controlled hemodynamic depression could be maintained with isoflurane–oxygen, but the frequency of myocardial lactate production before and after perfusion was greater than with other general anesthetics. Isoflurane dilated portions of the coronary bed but, because anaerobic metabolism occurred concomitantly, the theory that redistribution of flow can take place resulting in ischemic areas of ventricle is supported.

Key Words: ANESTHETICS, VOLATILE—isoflurane. SURGERY, CARDIOVASCULAR.

Myocardial oxygen balance during anesthesia is of critical importance in all patients, but especially in patients with coronary artery disease. As the newest major inhalational agent, isoflurane (1) must be compared in this respect with the other two potent inhalation anesthetics, halothane (2) and enflurane (3), and with intravenous anesthesia with fentanyl (4). Sybert et al. (5) raised the question of whether isoflurane may be detrimental to myocardial oxygenation, after documenting its coronary vasodilating action in dogs. Gelman et al. (6) also saw in the dog that myocardial blood flow increased with isoflurane, despite reduction of blood pressure and cardiac output, indicating coronary vasodilation with a possible "steal effect." In 1983 Reiz et al. (7) found that isoflurane was a potent coronary vasodilator in humans. In patients with coronary disease having major vascular operations, 1% isoflurane decreased coronary resistance, blood pressure, and cardiac output. Ten of 21 patients developed ECG or metabolic evidence of myocardial ischemia. In patients having coronary artery bypass grafts (CABG), Larsen et al. (8) found similar hemodynamic changes without ischemia, on induction with isoflurane–nitrous oxide, but later, on sternotomy, three of ten hearts showed global anaerobic metabolism. We have reported hemodynamic effects and effects on coronary sinus blood flow (CBF), myocardial oxygen consumption (MV_{O_2}) and lactate extraction (MLE) of halothane or morphine (2), enflurane (3), and fentanyl (4) anesthesia in patients having CABG. We now add a study of the myocardial metabolic effects and the hemodynamic effects of isoflurane–oxygen anesthesia in ten patients having CABG surgery before induction of anesthesia, through anesthesia and for 24 hr postoperatively. Our evidence supports the conclusion that isoflurane can cause coronary vascular dilation and can compromise myo-

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cardial oxygenation in patients with coronary arterial disease.

Methods

Patients Studied

Eight males and two females signed informed consent to the study that was approved by the institutional Ethics Committee. The patients' mean age was 54.8 yr (range 37–67), and weight 78.1 kg (range 63.5–93.2). NYHA disability was class II in two, III in six, and IV in two patients; six had known infarctions. All patients were candidates for CABG with ventricular function preserved, although nine had hypokinetic or akinetic areas. An average of 2.8 coronary arterial grafts (range 1–5) were inserted. At cardiac catheterization, cardiac index (CI) averaged 2.61 $L{\cdot}min^{-1}{\cdot}m^{-2}$ (range 1.60–3.40), left ventricular and diastolic pressure 14.7 mm Hg (range 9–22), and ejection fraction 0.61 (range 0.50–0.83). All patients were normotensive. Until the operation all patients were treated with effective doses of β-adrenergic blocking drugs (predominantly propranolol); one was also taking digoxin and a diuretic and another a diuretic. Three had been treated with nifedipine, which was discontinued 48 hr preoperatively and replaced with nitroglycerin paste.

Investigative Protocol

Premedication was with diazepam, 11.5 mg (range 10–15) and morphine, 15.2 mg (range 12–20). To enhance sedation in the operating room, additional intravenous diazepam, 5.5 mg (range 2.5–10) was given. Under local anesthesia a 20-gauge radial arterial catheter was inserted, followed by insertion of two thermodilution catheters through the right internal jugular vein: one was placed in the pulmonary artery (9), the other was manipulated into the mid-coronary sinus with fluoroscopy and its position adjusted by injecting contrast medium (10). By thermodilution, the latter catheter measures total CBF, almost all of which is left coronary inflow (11) and enables sampling of venous outflow from left ventricular muscle.

After a quiet period after instrumentation, the control data were obtained with the patient breathing air. Each study period included measurements of cardiac output (duplicate) and CBF, as well as measurements of arterial and central pressures, recording of ECG lead V, obtainment of arterial and coronary sinus CS) blood samples for measurement of oxygen saturation and hemoglobin (by co-oximetry), and lactate concentration (Boehringer Mannheim, Canada, Ltd.). Studies were repeated after induction of anesthesia, after intubation, before and after sternotomy, twice after cardiopulmonary bypass, and at 1 and 24 hr postoperatively. Calculated data (12) included MV_{O_2}, oxygen consumption of the left ventricle: the product of CBF and the arterio–CS difference of oxygen content, and MLE, the amount of arterial lactate extracted by ventricular muscle, i.e., arterial–CS lactate difference divided by arterial lactate content, expressed in percent. Analysis of variance and paired *t*-tests were used to determine statistical significance. A P value of less than 0.05 was considered to represent significance.

Anesthetic Protocol

Induction was initiated with thiopental, average dose 130 mg (range 100–200), followed by isoflurane and oxygen for an average of 12 min (range 7–17) before the second study. Systolic blood pressure was reduced by 30% from the awake level and maintained at the lower level using an inspired isoflurane concentration averaging 1.76% (range 0.67–3.8) over the duration of induction. Pancuronium, 0.1 mg/kg, was given and ventilation controlled to maintain Pa_{CO_2} (awake 43 mm Hg, after induction 45 mm Hg). After the postinduction study, isoflurane–oxygen was continued in concentrations adequate to keep blood pressure slightly below normal. Two patients were given nitroglycerin by infusion after the poststernotomy study because of ST depression or elevated pulmonary capillary wedge pressure (PCWP); one patient needed nitroglycerin again after cardiopulmonary bypass. No intravenous fluids were given during induction other than as drug vehicle, but the usual amounts of fluids and blood were infused during and after the operation.

Results

Duration of anesthesia averaged 299 min (range 216–400), duration of cardiopulmonary bypass (at 26°C) averaged 117 min (range 48–188), and aortic cross-clamp time averaged 44 min (range 11–86). Postoperatively, the time to first response to verbal command averaged 65 min (range 10–170) and the time to extubation 11.2 hr (range 3.5–24). Six patients were given nitroprusside for hypertension immediately after the 1-hr postoperative study. One patient required a dopamine infusion before and after another thoracotomy 10 hr postoperatively for bleeding. There were no ECG signs of infarction after the operation; all patients recovered and were discharged.

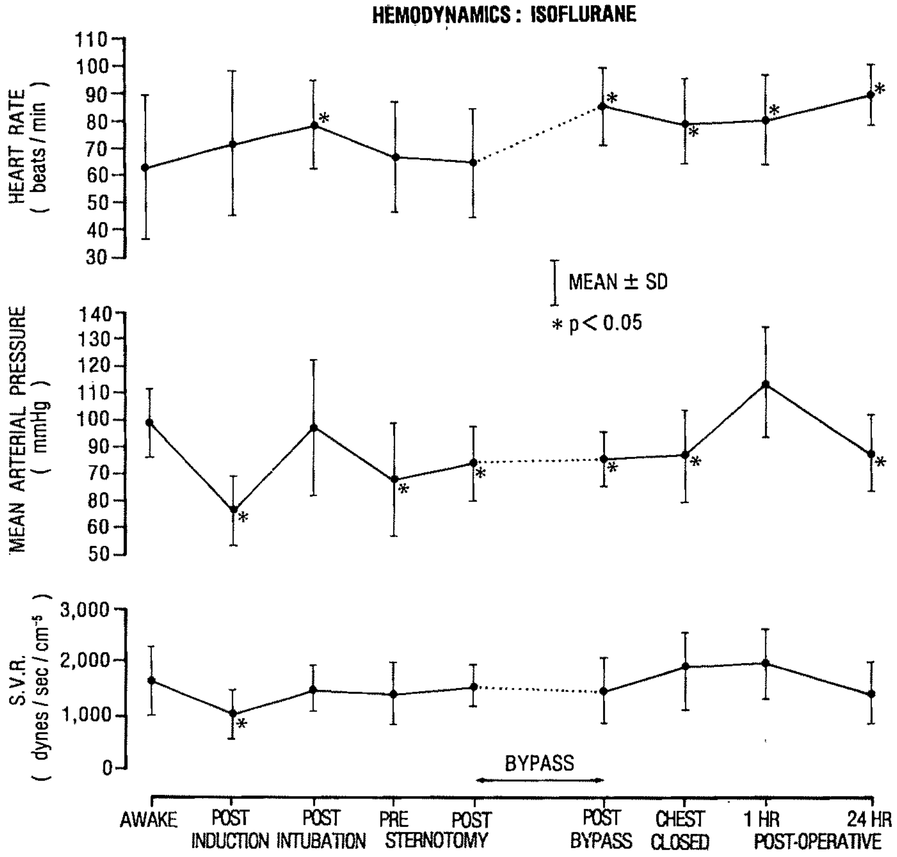

Figure 1. Heart rate, mean arterial pressure, and systemic vascular resistance before and at eight subsequent intervals after induction of isoflurane–oxygen anesthesia. SVR decreased only after induction.

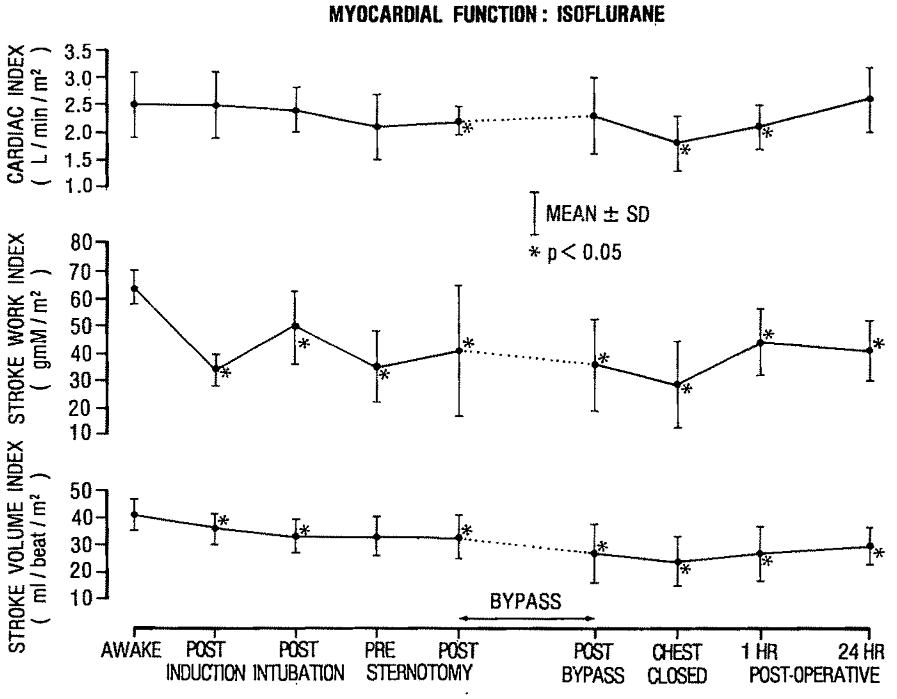

Figure 2. Cardiac, stroke work and stroke volume indices awake, during isoflurane–oxygen anesthesia, and twice postoperatively. Stroke work remained decreased throughout.

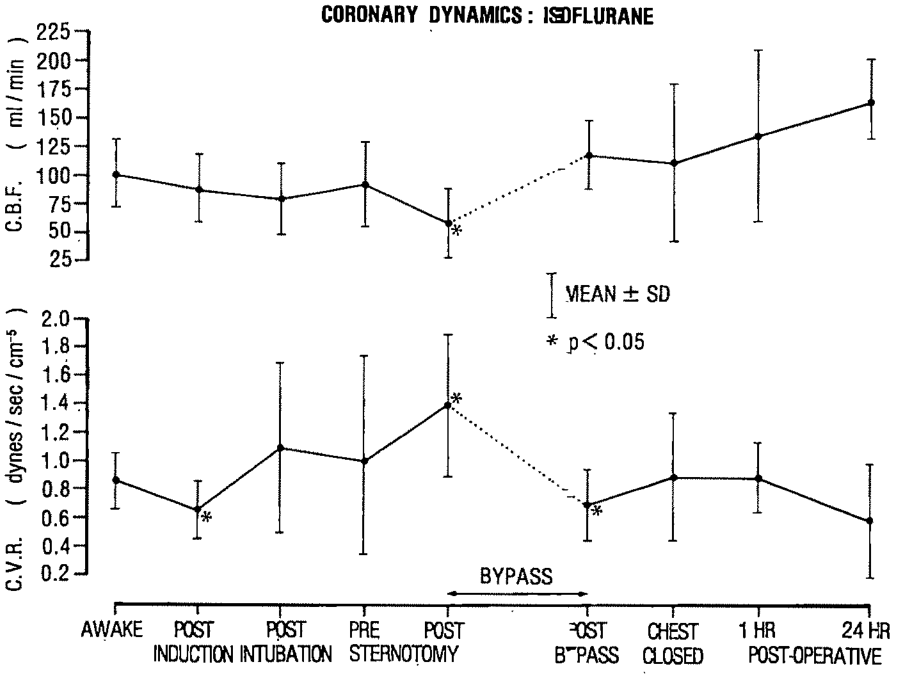

Figure 3. Total coronary sinus blood flow (CBF) and coronary vascular resistance (CVR) before, during, and after isoflurane–oxygen anesthesia. CBF did not decrease on induction when blood pressure did; CVR was significantly reduced.

Hemodynamics

Heart rate increased after intubation and then returned to awake levels; it remained elevated after cardiopulmonary perfusion (Fig. 1). Mean arterial pressure (MAP) was decreased 33% on induction; it returned to awake level on intubation. Subsequently, isoflurane was used to keep MAP below awake levels throughout anesthesia. The decrease in MAP on induction was due to lowered systemic resistance (SVR), but after intubation SVR remained at awake levels. The PCWP before induction averaged 16 mm Hg (range 11–23) and right arterial (RA) pressure averaged 10 mm Hg (range 6–14); neither changed during the study.

Cardiac index was stable until after sternotomy when it decreased slightly (Fig. 2). The CI also decreased toward the end of operation and the early recovery period. Stroke work index (SWI) paralleled changes in MAP with a decrease on induction, which continued throughout anesthesia and surgery. Stroke volume index remained decreased throughout anesthesia and surgery.

Myocardial Oxygenation

CBF in the awake patients averaged 103 ± 29.7 (SD) ml/min (Fig. 3). It did not decrease in response to the decrease in MAP on induction, but it did so after sternotomy when MAP and CI both were reduced. Coronary vascular resistance (CVR) decreased 23% on induction but increased after sternotomy above awake levels at a time when CBF was at its lowest point. CVR was also below awake levels immediately after bypass.

Oxygen content of coronary venous blood (CSo_2) increased 56% on induction and remained elevated until sternotomy (Fig. 4). It was also above preinduction levels 24 hr postoperatively. MVo_2 decreased on induction as the arterio–CS difference in oxygen content decreased; MVo_2 was below awake level both before and after bypass.

Arterial lactate levels increased on induction and continued to increase before bypass; both arterial and CS lactate levels were elevated after bypass (Fig. 5). Mean MLE decreased to 6% on induction, but then remained at 25% until cardiopulmonary bypass. However, individual patients showed wide variations in lactate exchange. One patient in whom there was myocardial lactate production when awake had an even greater amount of production after induction; extraction appeared after intubation and continued thereafter. Two other patients had myocardial lactate production on induction; in one it lasted through intubation. Myocardial lactate production occurred in two patients early after bypass and in two others after chest closure, with one heart still producing lactate 1 hr postoperatively. When awake, 1-mm ST segment depression in the V5 lead was present in three patients, and in two patients 2-mm depression occurred. In two of these patients ST depression was increased by intubation; two others developed depression after sternotomy; the remaining six patients showed es-

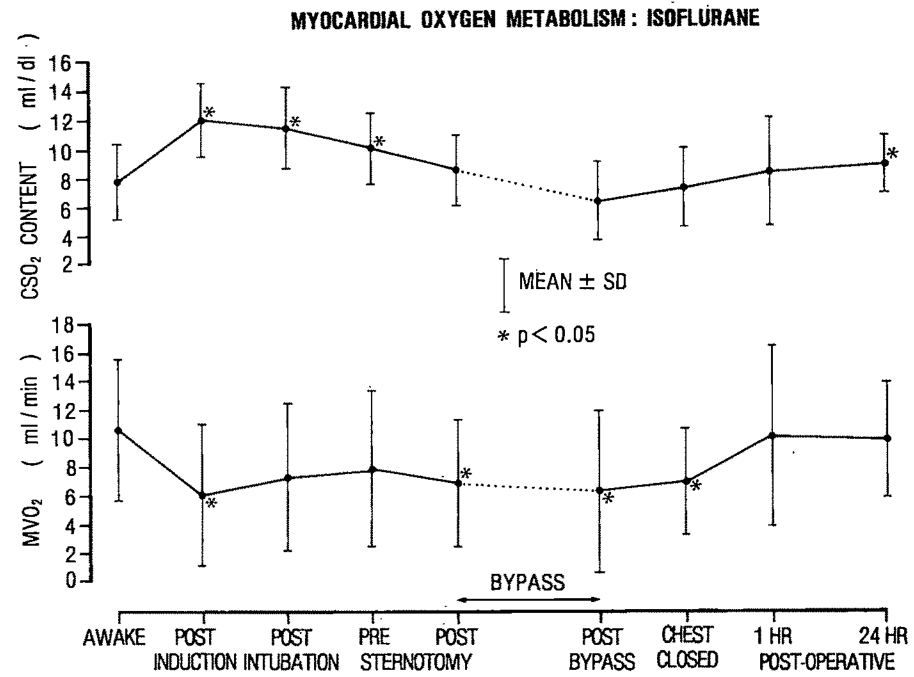

Figure 4. Oxygen content of CS blood (CSo_2) increased on induction of isoflurane–oxygen anesthesia and remained so until sternotomy. Myocardial oxygen consumption also decreased on induction.

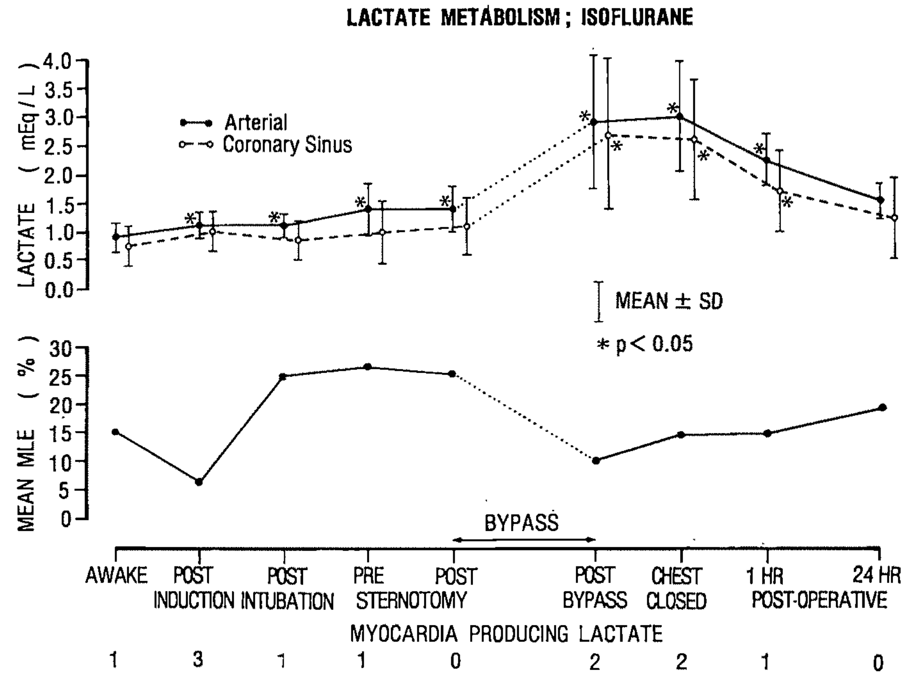

Figure 5. Arterial lactate levels increased throughout isoflurane–oxygen anesthesia, but CS lactate levels increased only after conclusion of cardiopulmonary bypass. Myocardial lactate production occurred in three patients after induction and was present in one or two patients at most subsequent studies.

sentially no change. There was no correlation between ST segment changes and myocardial lactate production.

Discussion

Since 1979 three groups of clinical investigators have made significant progress in quantitating coronary blood flow and myocardial oxygen balance in humans, as related to hemodynamic effects of the major anesthetic drugs. Sonntag et al. (8,13–15) have used the argon washin technique of measuring coronary flow with CS sampling, while Reiz et al (7,16–18) and Moffitt et al. (2–4) have utilized thermodilution CS catheters (10). From these multiple studies a commonly accepted and applied principle has been validated: preservation of oxygen supply distal to coronary lesions requires an anesthetic technique that prevents MVO_2 from increasing. Heart rate and blood pressure must be kept at or below that of the quiet, awake state. That halothane (2,13,17) and enflurane (3,8) can be given to β-blocked coronary patients to maintain controlled hemodynamic depression and preserve myocardial oxygenation has been shown. However, enflurane anesthesia sufficiently deep to reduce systemic blood pressure by 50%, in non-β-blocked patients, can cause myocardial ischemia (18). Two reports (4,14) document that high-dose fentanyl does not always maintain a hypodynamic circulation, thus risking ischemia. Isoflurane must be examined by the same criteria relative to its appropriateness for patients with coronary arterial disease. Reiz et al. (7) have reported that isoflurane reduced coronary resistance significantly in patients with coronary artery disease, with evidence of myocardial ischemia. Larsen et al. (8) also reported ischemia (lactate production) in three of ten CABG patients after sternotomy. Continuing our systematic investigation of coronary flow and myocardial oxygenation with different general anesthetics, the present study describes results obtained when isoflurane–oxygen anesthesia is used for patients having CABG surgery.

Accuracy and Limitations of Our Methods

From duplicate determinations in awake patients done 2–3 min apart, and from comparison of our data with those of Reiz and Sonntag, we conclude that measurement of total coronary sinus flow by thermodilution is accurate. CBF essentially represents venous outflow from left ventricular muscle and thus, left coronary inflow; it changes constantly depending on local tissue oxygen need (19). CBF is a mean global left ventricular flow over 20 sec, with a major influence being arterial pressure during that period (4). Wide variations in CBF must exist in regional flow distal to coronary occlusions and stenoses. The same limitation applies to oxygenation: blood from the coronary sinus predominantly reflects the greater outflow from adequately oxygenated segments of left ventricular myocardium. In this venous blood, lactate from anaerobic glycolysis in muscle distal to coronary lesions may not be evident. However, when CS blood contains more lactate than the arterial blood, widespread ischemia must be present in left ventricular muscle.

All our studies have followed a uniform protocol and method, including careful placement of the catheter to measure total left ventricular, and not regional left ventricular, coronary blood flow. The patients entering each study have been quite uniform: candidates for CABG with preserved ventricular function on β-blockade but without other complicating cardiac problems or hypertension. With the same principles and practices used for the studies of halothane, enflurane, and isoflurane, comparing results in the three groups is possible.

Hemodynamic Responses

Others have published data on the circulatory effects of isoflurane in animals (5,20) and in humans with coronary disease (21). There have been three studies of CBF, CVR, and MVO_2, correlated to hemodynamics, those of Reiz et al. (7,22) and Larsen et al. (8). In our present study, induction with isoflurane involved a mean inspired concentration of 1.76% over a mean of 12 min, to purposely decrease systolic arterial pressure by 30%. The latter was entirely the result of systemic vascular dilation because cardiac index and heart rate did not change. With this decrease in afterload and no change in heart rate or wedge pressure, a major increase in cardiac index should have occurred. That it did not increase supports the conclusion that isoflurane is a potent depressant of pumping function. It was possible to keep blood pressure in steady mild depression and heart rate slow during the course of anesthesia, effects like those seen with halothane and enflurane. Cardiac index decreased only after sternotomy; whereas with enflurane, blood pressure control was due to continuously reduced cardiac performance. Stroke work with isoflurane remained well below that when patients were awake; similar effects occurred with enflurane and halothane.

While means for the group indicate satisfactory hemodynamic control after induction with isoflurane, induction was not always smooth compared to inductions with halothane and enflurane: three patients developed a hyperdynamic circulation. One of these three patients, one whose nifedipine had been discontinued, had a severe increase in blood pressure, heart rate, and PCWP in the first 5 min. It took ten more minutes of high concentration of isoflurane to produce a 25% decrease in systolic arterial pressure below awake level. The second patient, bradycardic initially, developed a sudden tachycardia to 130 beats/min with ST depression (3 mm) but without hypertension during induction. After a 16-min induction, with a high concentration of isoflurane, the desired reduction in systolic pressure was finally achieved, with the heart rate slowed to 108 beats/min. In the third patient, PCWP increased precipitously early in induction without change in blood pressure or heart rate; PCWP gradually decreased to awake level (18 mm Hg) after intubation. Two other patients studied using this protocol were excluded from group analysis: one was hypertensive preoperatively and the other was taking only nifedipine. Both still had hyperdynamic circulations after induction. Although during this period, local practice included discontinuing calcium blocking agents preoperatively, which may have affected two patients, this incidence of increases in blood pressure and heart rate has not been seen with any of our other anesthetic studies. We conclude that isoflurane alone is not satisfactory for induction of anesthesia in patients with coronary artery disease even after thiopental.

Myocardial Oxygenation

Several aspects of induction with isoflurane–oxygen are strikingly different compared to halothane and enflurane. First is that CBF decreased a statistically insignificant 16% at a time when mean blood pressure was reduced 33%. Like cardiac index, CBF remained unchanged, so calculated coronary resistance decreased a significant 23% ($P < 0.05$). CVR later increased as CBF was reduced after sternotomy. We have not documented a significant decrease in coronary vascular resistance with any other anesthetics (2–4).

A second difference from other agents given alone (2–4) is the much larger increase (56%) in oxygen content of CS blood after induction, which elevation continued through sternotomy, unlike the changes in CSO_2 content seen with other anesthetics. In addition to less oxygen extracted due to reduced cardiac work, the coronary bed that could dilate during isoflurane anesthesia apparently did so, keeping CBF at awake level in spite of reduced perfusing pressure. The decrease in MVO_2 with isoflurane was present also with halothane and enflurane.

The third dissimilarity with isoflurane is the greater incidence of evidence of myocardial ischemia, i.e., lactate production. Three patients had myocardial lactate production after induction with isoflurane compared with one of ten induced with fentanyl (4), one of twelve induced with halothane (2), and none when induction was with enflurane (3). The incidence of ischemia at subsequent study times throughout anesthesia with isoflurane was also greater than with the other agents. Two of the three patients previously described with stormy inductions showed myocardial lactate production in the presence of CS oxygen contents after induction that were 55 and 90% greater than when awake. A portion of their coronary bed must have been widely dilated, but areas of muscle must have had insufficient oxygen, with anaerobic glycolysis. Presumably these were muscle segments distal to coronary lesions that were unable to dilate. This supports the thesis that coronary steal can occur with isoflurane.

Comparison with Other Evidence

The three other studies (7,8,22) of hemodynamic function and myocardial oxygenation during isoflurane anesthesia are not directly comparable to ours due to differences in protocol. Reiz et al. (7) gave 70% nitrous oxide during induction, but after intubation adjusted F_{IO_2} with nitrogen to maintain arterial oxygen tension at preanesthetic levels. Their study was after 30 min of 1% end-tidal isoflurane, following intubation. Our study was before intubation after 12 min of 1.76% inspired isoflurane with oxygen. They found decreases in MAP, CI, PCWP, and SVR, with an increase in heart rate. CBF did not change, so CVR decreased 26%; MVO_2 and MLE both decreased. Evidence of ischemia consisting of ST depression or T-wave inversion appeared in 10 of 21 patients. This suggested regional ischemia due to reduced perfusing pressure and coronary flow redistribution. Other differences between their study and ours include that our patients were premedicated before instrumentation and were receiving larger doses of β-blocking drugs, with slower pulse rates when awake. However, both studies found global left ventricular ischemia: 10 of 21 in one study and 3 of 10 patients in the other, with the anesthetic agent seemingly the most likely cause in both.

Reiz and Ostman (22) have also studied the effects of isoflurane (1.5 MAC) given with 70% nitrous oxide for approximately 45 min to patients with ischemic heart disease. MAP decreased 45%, SVR 40%, and CI 17%. CSF was unchanged, but CVR decreased 40%. Seven of 11 patients developed ST segment changes, with lactate production seen in one patient. This protocol also differed from ours in the greater length and depth of anesthesia (greater reduction in MAP), the lesser F_{IO_2} (30% O_2) and the presence of nitrous oxide with its additive detrimental effects on hemodynamic function (23,24).

In the protocol of Larsen et al. (8), nitrous oxide, which was given throughout, might also have had significant detrimental effects on both hemodynamics and myocardial oxygenation. On induction they saw decreases in MAP (24%), CI (19%), CBF, and MVO_2, with an increase in heart rate. During sternotomy, CBF and MVO_2 increased to preinduction levels. Three of ten myocardia produced lactate, the same incidence as ours. While all of these three protocols involved PaO_2 considerably less than that in our patients receiving oxygen, myocardial ischemia occurred in all three studies. Ischemia was not due primarily to the level of inspired oxygen.

Was It the Drug or the Study Protocol?

A pertinent question is whether myocardial ischemia found in these studies was due to the isoflurane alone (a drug effect) or to the ways that it was given (the study protocol) or to a combination of both factors. In studying effects of inhaled anesthetics on human hemodynamic function, one can give a fixed concentration (e.g., 1 MAC) for a set time (e.g., 30 min) and measure effects (e.g., MAP, CI, CBF, CS oxygen and lactate contents). This was the method followed by Reiz et al. We followed an alternate method of giving the anesthetic agent to a specific end-point effect (30% decrease in systolic arterial pressure from awake level), thus using different concentrations for each patient's induction.

The hemodynamic changes in the studies by Reiz et al. were greater than in our postinduction state, which would create more potential for producing coronary vasodilation and possibly ischemia. Other factors may have influenced their incidence of ischemia: relative absence of β-blockade, the 30% inspired oxygen concentration, and nitrous oxide (when used). So the magnitude of hemodynamic change resulting from the protocol possibly was responsible for the effects on myocardial oxygenation.

Can the same conclusion be made relative to our study protocol? We are not all sure. We studied as uniform a group as possible: patients needing vein grafts but having good ventricular function. Because a decrease in blood pressure is commonly produced on induction in these patients, a 30% decrease was chosen as a reasonable, clinical end-point, fixed for each, because the anesthetic concentration was not uniform. In addition, all our previous data verify the safety of that end-point for myocardial oxygen balance in this patient population. With this moderate change in blood pressure from isoflurane in oxygen, myocardial lactate production occurred in three patients. This is three more than seen with enflurane given under the same protocol, with the same 30% reduction in blood pressure on induction. It cannot be accepted that the evidence of ischemia in our patients was predominantly due to the way it was given. Isoflurane, in concentrations not producing severe hemodynamic depression, has the capability of dilating the coronary vascular bed in coronary patients with preserved ventricular function.

Although isoflurane produced these findings when given alone, the drug is not generally used alone in cardiac patients. When combined with other agents such as moderate-dose fentanyl, it quite possibly will show the same stable control of hemodynamics and preservation of myocardial oxygenation, in this class of patient, as we have found with fentanyl–enflurane (25) and fentanyl–halothane (26). That study is in progress.

Summary

We found that isoflurane–oxygen alone is not ideal for therapeutic depression of the circulation during induction in premedicated patients undergoing CABG surgery. Although it was possible to maintain steady hemodynamic depression during anesthesia, isoflurane–oxygen decreased coronary resistance significantly, and evidence of ischemia (myocardial lactate production in 30% of patients) indicated that significant myocardial oxygen deficiency can occur.

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Pulmonary Vascular Responses to Nitrous Oxide in Newborn Lambs

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EISELE JH Jr, MILSTEIN JM, GOETZMAN BW. Pulmonary vascular responses to nitrous oxide in newborn lambs. Anesth Analg 1986;65:62–4.

The hemodynamic effects of N_2O and N_2O plus hypoxia were studied in six lambs (0–3 days of age) that were instrumented with pulmonary artery flow probes and catheters, as well as aortic and left atrial catheters. N_2O was administered to the awake lambs through a mask in mixtures of 75% N_2O:25% O_2 and 75% N_2O:11% O_2:14% N_2. Pulmonary arterial pressure and resistance increased significantly upon exposure to N_2O both during normoxia and hypoxia, and nitrous oxide also significantly elevated left atrial pressure and decreased pulmonary artery blood flow during normoxia. Aortic pressure was essentially unchanged by nitrous oxide. The data indicate that in newborn lambs the pulmonary vasculature responds to N_2O with vasoconstriction.

Key Words: ANESTHETICS, GASES—nitrous oxide. LUNG—blood flow. HYPOXIA—pulmonary vascular response.

Nitrous oxide has been shown to have physiologic effects on the cardiovascular system. In addition to direct myocardial depression (1), nitrous oxide causes sympathetic stimulation by increasing sympathetic outflow from the brain (2) and by inhibiting norepinephrine removal by the lung (3). In adult animals the increase in sympathetic activity counterbalances the myocardial depression and also alters or increases systemic and pulmonary vascular resistance.

Because the newborn has a relatively thick and reactive muscular medial layer in pulmonary arterioles (4), its pulmonary vasculature may be more responsive to nitrous oxide than that of adults. This could have important clinical implications in anesthetized newborns because an increase in the pulmonary vascular resistance (PVR) may be beneficial to premature neonates with low PVR and a left-to-right shunt across a patent ductus arteriosus, whereas such an increase in PVR may be detrimental to the more mature neonate with the persistent pulmonary hypertension syndrome or to the newborn in whom the PVR has not yet decreased.

Because the pulmonary vascular effects of nitrous oxide have not been evaluated in newborns, we studied the pulmonary vascular response to nitrous oxide in newborn lambs with both normal and elevated PVR.

Materials and Methods

Six newborn lambs (0–3 days of age) were calmed with a blindfold, placed under halothane anesthesia by mask, intubated, and ventilated with a Baby Bird Respirator. Utilizing sterile surgical technique, a jugular venous catheter was placed. A left thoracotomy was then performed, followed by placement of catheters in the main pulmonary artery, left atrium, and aorta, while an electromagnetic flow probe was fitted on the main pulmonary artery. The ductus arteriosus was noted to be closed in each lamb. The catheters were flushed with a heparinized solution, plugged, and tunneled subcutaneously along with the flow probe cable and exited at an interscapular site, where they were secured in a mesh pouch.

After recovery (1–2 days), studies were performed on each lamb while it was awake and blindfolded in a sling restrainer apparatus. Gas mixtures were analyzed and delivered via a plastic headmask at flows high enough to prevent rebreathing. Continuous measurement of the mean pulmonary arterial pressure (P_{PA}), mean left atrial pressure (P_{LA}), mean aortic pressure (P_{AO}), and mean pulmonary blood flow ($\dot{Q}_P$) was performed.

The baseline PVR was normalized by delivering a 25% oxygen mixture balanced with nitrogen (25:75) or elevated by delivering an 11% oxygen mixture bal-

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Table 1. Hemodynamic Data Averaged for 6 Lambs (±SEM)

	Control	N_2O (75%)	Hypoxia	N_2O (75%) plus hypoxia
PPA (mm Hg) mean	24.1 ± 3.2	29.0 ± 4.0	40.3 ± 6.6	47.8 ± 5.7
(change)		(+20.3%)[a]		(+18.6%)[b]
$\dot{Q}$P ($L \cdot min^{-1} \cdot kg^{-1}$) mean	0.180 ± 0.031	0.146 ± 0.024	0.256 ± 0.034	0.263 ± 0.036
(change)		(−18.8)[c]		(+2.7%)
PVR (R units) mean	116.4 ± 22	157.7 ± 27	157.5 ± 22	185.7 ± 24
(change)		(+35%)[a]		(+18%)[b]
PAO (mm Hg) mean	73.5 ± 4	71.6 ± 3	76.7 ± 4	76.5 ± 3
(change)		(−2.5%)		(−0.2%)
PLA (mm Hg) mean	−0.3 ± 2	+2.5 ± 1[c]	−0.2 ± 2	+1.4 ± 1.1

[a] $P < 0.01$.
[b] $P < 0.02$.
[c] $P < 0.05$.
Abbreviations: PPA, pulmonary artery pressure; $\dot{Q}$P, pulmonary blood flow (cardiac output); PVR, pulmonary vascular resistance; PAO, aortic pressure, PLA, left atrial pressure.

anced with nitrogen (11:89). The PVR was determined in the classical fashion as mean PPA minus mean PLA divided by mean $\dot{Q}$P. The pulmonary vascular response to nitrous oxide was assessed in the lambs under normoxic conditions using an oxygen:nitrous oxide mixture (25:75) and under hypoxic conditions using an oxygen:nitrous oxide:nitrogen mixture (11:75:14).

Lambs were randomly given two exposures of each gas mixture with sufficient time between exposures for hemodynamic recovery. The data for repeat exposures was averaged for each lamb and shown on Table 1 as the mean values for six lambs for each variable with the standard error of the mean. Statistical analysis was performed using a two-tailed nonparametric test (Wilcoxin signed ranks) incorporating the data from all exposures. Significance was established at P values less than 0.05.

Results

The six lambs studied under normoxic conditions had arterial oxygen tensions greater than 60 torr. Baseline mean PPA was 24.1 ± 3.2 torr; the mean PVR, 116.4 ± 22 resistance (R) units; mean PLA, −0.3 torr; mean $\dot{Q}$P, 0.180 ± 0.03 $L \cdot min^{-1} \cdot kg^{-1}$; and mean PAO, 73.5 ± 4 torr. The mean PPA increased to 29.0 ± 4.0 torr ($P < 0.01$), PVR increased to 157.7 ± 27 R units ($P < 0.01$), PLA increased to +2.9 torr ($P < 0.05$), and $\dot{Q}$P decreased to 0.146 ± 0.02 $L \cdot min^{-1} \cdot kg^{-1}$ ($P <$ 0.05), whereas PAO changed only from 73.5 ± 4 to 71.6 ± 3 torr during nitrous oxide (Table 1).

Under alveolar hypoxic conditions the lambs had mean arterial oxygen tensions of 31 torr. Baseline mean PPA was 40.3 ± 6.6 torr; mean PVR, 157.5 ± 22 R units; mean PLA, −0.2 torr; mean $\dot{Q}$P, 0.256 ± 0.03 $L \cdot min^{-1} \cdot kg^{-1}$; and mean PAO, 76.5 ± 3 torr. During nitrous oxide exposure the PPA increased to 47.8 ± 5.7 torr ($P < 0.02$) and PVR increased to 185.7 ± 24 R units ($P < 0.02$) whereas the other hemodynamic variables did not change significantly (Table 1). The ductus arteriosus remained closed after the studies in all lambs.

Discussion

Nitrous oxide increased the PPA and PVR in both normoxic and hypoxic newborn lambs. This pulmonary vasoconstrictor action may be due to the sympathetic effects of nitrous oxide, which have been shown to increase sympathetic outflow from the brain (2) and to inhibit removal of norepinephrine by the lung (3). The calculated increases in PVR were larger during the normoxic N_2O exposure (+35%) than the hypoxic N_2O exposure (+18%) because during normoxia, N_2O produced a decrease (−19%) in cardiac output. This decrease in cardiac output may have been due to direct myocardial depressant effects of nitrous oxide during normoxia. This is supported by the increase in PLA during nitrous oxide. This did not occur during hypoxia when nitrous oxide was added. In fact, hypoxia alone increased cardiac output 42%, presumably due to its sympathetic effect. This could have masked any negative inotropic influence of nitrous oxide.

The nitrous oxide induced increase in transpulmonary vascular pressure (PPA–PLA) was greater during hypoxia than during normoxia (15% vs 8.6%) even though the PPA was considerably high during hypoxia before nitrous oxide was added. The cardiac output, however, did not change appreciably when nitrous oxide was added to hypoxia. Consequently, the calculated pulmonary vascular resistance increased with the addition of nitrous oxide to hypoxia but not to the same extent as when nitrous oxide was added to normoxia. In essence, nitrous oxide increased P_{PA} during normoxia and decreased $\dot{Q}_P$ whereas during hypoxia, it increased P_{PA} to a greater degree but did not change $\dot{Q}_P$. This observation does not clarify the mechanism by which nitrous oxide produces pulmonary vascular vasoconstriction, but it suggests that nitrous oxide acts in a similar and additive manner to hypoxia.

These findings are consistent with those observed in adult human patients with coronary artery disease (5) or moderate pulmonary hypertension secondary to mitral valve disease (6). In an elegant study, 16 patients with coronary artery disease with normal pulmonary dynamics were compared to 16 patients with mitral valve disease with elevated pulmonary artery pressures. The two groups differed in that the latter showed increases in pulmonary arterial and wedge pressures when nitrous oxide was introduced (7). In another study of patients with coronary disease and normal resting pulmonary artery blood pressures, there was no pulmonary vascular response to nitrous oxide (8). However, in that study nitrous oxide was used in conjunction with diazepam, which may have attenuated any sympathetic response. Our findings are in contrast with the findings reported in newborn piglets in which 75% nitrous oxide did not produce significant pulmonary hemodynamic changes. Unlike our study, pentobarbital, a central and cardiac depressant, was administered prior to nitrous oxide exposure.

Nitrous oxide appears to have both direct pulmonary vasoconstrictor action, and to a lesser extent, myocardial depressant effects in newborn lambs. These observations are supported by clinical reports. In children with increased pulmonary blood flow, 75% nitrous oxide significantly increased pulmonary artery blood pressure and pulmonary vascular resistance (9). In one infant with a ventricular septal defect, a patent foramen ovale, and infundibular stenosis, administration of nitrous oxide converted a left-to-right shunt to a bidirectional shunt. In another case, cardiovascular collapse occurred after the addition of nitrous oxide to the anesthetic in a 1-yr-old infant who had a right ventricular pressure of 82 torr secondary to anomalous pulmonary venous drainage (10). Whether or not similar effects occur in normal human neonates is unknown at this time, but caution is recommended when utilizing N_2O in human neonates who have evidence of persistent elevation of their pulmonary vascular resistances or myocardial dysfunction.

Human neonates are exposed to nitrous oxide not only directly during surgical procedures but also indirectly in the intrapartum period when N_2O may be administered to mothers in labor. An increase in PVR could be beneficial to the premature neonate with a left-to-right shunt across a patient ductus arteriosus. On the other hand, N_2O might be detrimental to the premature neonate with respiratory distress syndrome and ventilation-perfusion inequalities, or to the more mature neonate with pulmonary hypertension and the persistent fetal circulation syndrome, as well as to the newborn whose PVR has not yet made its usual decrease, even though the degree of PVR could not be considered pathologic under normal circumstances. Of course caution must be exercised when extrapolating results from studies on term lambs to premature lambs or humans.

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Pneumocephalus:

Effects of Patient Position on the Incidence and Location of Aerocele after Posterior Fossa and Upper Cervical Cord Surgery

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TOUNG TJK, McPHERSON RW, AHN H, DONHAM RT, ALANO J, LONG D. Pneumocephalus: effects of patient position on the incidence and location of aerocele after posterior fossa and upper cervical cord surgery. Anesth Analg 1986;65:65–70.

The incidence of pneumocephalus and factors contributing to its occurrence were studied retrospectively in 100 consecutive patients who underwent posterior fossa or cervical cord surgery in the sitting, park-bench, and prone positions. Supine skull x-ray films taken immediately postoperatively were used to determine the presence of intracranial air. Surgery in the sitting position uniformly resulted in pneumocephalus (32/32 patients). Pneumocephalus also occurred frequently among patients in the park-bench (29/40) and prone positions (16/28). Intraventricular air occurred more frequently when patients were in the sitting position (25/32) than in the two other surgical positions (3/29 and 4/16, respectively, P < 0.001). The high incidence of pneumocephalus and of intraventricular air that occurred when patients were in the sitting position is attributed to the large amount of cerebrospinal fluid drained due to gravitational effect. When surgical position is considered one of the contributing factors, only position significantly affected the frequencies of pneumocephalus and intraventricular air accumulation. None of the 77 patients with pneumocephalus suffered neurologic change related to the presence of intracranial air. We conclude the following: pneumocephalus commonly occurs after posterior fossa or cervical cord surgeries, particularly when the surgery is performed in the sitting position; neurologic change caused by pneumocephalus is a rare complication after posterior fossa craniotomy; when a patient with coexisting hydrocephalus undergoes surgery, if the patient is in the sitting position, there is an increased risk of trapping a large amount of intracranial air.

Key Words: SURGERY, NEUROLOGIC—pneumocephalus. ANESTHETICS, GASES—nitrous oxide. POSITION—pneumocephalus.

Tension pneumocephalus (symptomatic intracranial air) after posterior fossa craniotomy recently has been reported with increasing frequency (1–8). Although the incidence has been generally recognized as rare, the true incidence is unknown. On the other hand, pneumocephalus (asymptomatic intracranial air) is frequently demonstrated by postoperative skull-roentgen examination (9,10). Little information, however, is available concerning its incidence, especially after posterior fossa craniotomy. In order to understand the pathogenesis of tension pneumocephalus, this information is important. Therefore this study was carried out to address this issue in patients after a routine posterior fossa or upper cervical cord surgery performed in three commonly employed positions, and to analyze the possible contributing factors.

Materials and Methods

One hundred consecutive patients, ages 1 month to 76 yr, were studied. They underwent posterior fossa or intradural cervical spinal cord surgery performed in the sitting, park-bench, and prone positions from October 1983 to February 1985. The patients were divided into three groups and analyzed according to the patient's position during the surgery. In all patients, postoperative, supine, anteroposterior, and lateral (horizontal beam) skull x-ray films (11,12) were obtained 30–120 min after surgery. X-ray films of each patient were evaluated by a radiologist without knowledge of patient's clinical course, the position during surgery, or the intra- or postoperative course.

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Table 1. Effects of Position on Incidence of Pneumocephalus

Group	Position	Total number of patients	% With pneumocephalus
1	Sitting	32	100 (32/32)
2	Park-bench	40	73 (29/40)
3	Prone	28	57 (16/28)

Intracranial air distribution was classified as being one of the following: (12,13) fronto–parietal subdural; intraventricular; suprasella; or pontine cisterns. The distribution of intracranial air into these anatomical locations reflects the amount of air that had entered (14).

Medical and anesthesia records were evaluated for the following factors (3,15,16): patient's position; hydrocephalus with or without shunting procedure; nitrous oxide (N_2O) administration; intraoperative use of dehydrating agent (mannitol, furosemide, or both); and duration of surgery. These factors were compared with the previously reported cases of postoperative tension pneumocephalus. All data were analyzed statistically by χ^2-test.

Results

Thirty-two patients had surgery in the sitting position (group 1), 40 in the park-bench position (group 2), and 28 in the prone position (group 3). The ages of the patients in each group varied widely. There was no infant patient in group 1 (sitting position), probably because of technical difficulties.

Group 1—Sitting Position (n = 32)

This group consisted of four cases of upper cervical cord surgery and 28 cases of occipital craniectomy. All 32 patients developed pneumocephalus (100%). The incidence is significantly greater than in two other positions ($P < 0.05$) (Table 1). In all 32 patients, a large amount of air was located in the fronto–parietal subdural region. In 25 of the 32 patients, air was also found in the lateral and third ventricles (25/32, 73%); in 13 patients air was found in the suprasella cistern, and in 4 patients in the pontine cistern (Table 2). Twenty-two of the 32 patients had preoperative hydrocephalus (69%) but only eight patients had either ventriculoperitoneal shunt (V–P) or intraoperative drainage procedures. Of these 22 patients, 17 had intraventricular air (17/22, 77%); in each of the remaining five patients who did not have intraventricular air the tumor either compressed the fourth ventricle or obstructed the aqueduct. The presence of intraventricular air in this position is significantly greater ($P < 0.001$) than that associated with other positions. In this group each developed pneumocephalus, regardless of whether the patient had nitrous oxide anesthesia and received mannitol (Table 3). The operative time in this group was 5.9 ± 2.2 hr (mean ± SD).

Group 2—Park-Bench Position (n = 40)

Twenty-nine patients in this group developed pneumocephalus (73%) (Table 1). In 23 patients, air was located in the fronto–parietal area, in five patients in the suprasella cistern only, and in one patient in both the suprasella and pontine cisterns. The aerocele in this group was considerably smaller than it was in group 1. Of the 23 patients with air in the fronto–parietal region, seven patients also had air in the suprasella cistern, but only three patients of 29 patients with pneumocephalus had intraventricular air (10%, Table 3). As for possible contributing factors, there was no difference statistically in the incidence of postoperative pneumocephalus between patients with and without the factors evaluated (Table 3).

Group 3—Prone Position (n = 28)

There were four cases of cervical dorsal-root-entry-zone (DREZ) lesions included in this group. In this group, 16 patients (57%) developed pneumocephalus. All four patients with cervical DREZ developed pneumocephalus. Of the 16 patients with pneumocephalus, nine patients had air in both the frontal subdural and suprasella cistern, four had air in both frontal subdural and lateral ventricles, one had air only in the suprasella region, and one showed air only in the pontine cistern. Thus in this group four patients had intraventricular accumulation of air (4/16, 25%; Table 3). Of the contributing factors studied, preoperative hydrocephalus and N_2O anesthesia did not play significant roles in the development of pneumocephalus (Table 3). However none of the 16 patients who developed pneumocephalus received mannitol intraoperatively (Table 3). Operative times were not statistically different between patients in group 3 who did and those who did not develop pneumocephalus (5.0 ± 2.2 and 5.1 ± 2.4 hr, respectively, mean ± SD). None of the 77 patients with pneumocephalus developed neurologic symptoms related to the presence of intracranial air.

Because the review of all reported cases of tension pneumocephalus after posterior fossa craniotomy revealed that the information for each factor was in-

Table 2. Distribution of Intracranial Air

Group	Surgical Position	Fronto–parietal subdural (number of cases)[a]	Intraventricular (number of cases)[a]	Cisternal (number of cases) Suprasellar[a]	Pontine[a]
1	Sitting	32/32	25/32[b]	13/32	4/32
2	Park-bench	23/29	3/29	12/29	3/29
3	Prone	10/16	4/16	10/16	3/16

[a] Numbers are the number of patients with air in the anatomic location/total number of patients with pneumocephalus.
[b] $P < 0.001$ compared to groups 2 and 3.

Table 3. Incidence of Pneumocephalus Related to Contributing Factors

	History of hydrocephalus		Administration of N_2O		Administration of mannitol	
Position	Yes	No	Yes	No	Yes	No
Sitting ($n = 32$)	100% (22/22)	100% (10/10)	100% (13/13)	100% (19/19)	100% (3/3)	100% (29/29)
Park-bench ($n = 40$)	75% (9/12)	71% (20/28)	81% (17/21)	63% (12/19)	63% (10/16)	79% (19/24)
Prone ($n = 28$)	69% (6/10)	56% (10/18)	50% (11/22)	83% (5/6)	0% (0/8)	80% (16/20)

Table 4. Comparison of the Contributing Factor of Tension Pneumocephalus between Present Study and Reported Cases (23)

	Duration of surgery (hr, mean ± SD)	Hydrocephalus preoperative[a]	Intraoperative use of mannitol[a]	Intraoperative Pa_{CO_2} (torr, mean ± SD)
This study	5.7 ± 2.2[b]	37/77	13/77	26.4 ± 3.3–32.5 ± 6.5
Case reports	8.4 ± 1.2	2/4	1/4	26.3 ± 2.6–34 ± 3.4

[a] Number of patients with contributing factor/total number of patients with pneumocephalus.
[b] $P < 0.05$.

complete, comparison was made only with our previously reported cases of tension pneumocephalus (8). The comparison revealed that only the duration of the surgery differs significantly (Table 4).

Discussion

We have confirmed the previous finding that pneumocephalus occurs frequently in posterior fossa surgery performed in the sitting position (6). Additionally, we have shown a high incidence of pneumocephalus in patients after the surgery performed in park-bench and prone positions. The difference in position in the incidence of pneumocephalus is probably related to the amount of cerebrospinal fluid (CSF) drained during surgery and also to the location of CSF drainage relative to the remainder of the head. Gravity causes a larger amount of CSF to be drained in the sitting position than in the other surgical positions. This gravitational effect is more serious in the presence of hydrocephalus. Because an abnormally larger amount of CSF is present in patients with hydrocephalus, a proportionally greater volume of CSF can be drained. Therefore in the presence of hydrocephalus, there is increased potential for accumulation of a large amount of air. The additive effect of hydrocephalus to the sitting position is seen in the significantly higher incidence of intraventricular air accumulation in the group 1 patients than patients in the two other groups ($P < 0.001$). It appeared that when surgery is performed with patients in the sitting position, hydrocephalus tends to augment the entrainment of larger air volume.

The mechanism of air entrainment can best be explained by the principle of positional and anatomic relations utilized during pneumoencephalography. The sitting position employed for posterior fossa craniotomy is analogous to the position for pneumoventriculography (14); i.e., the neck is moderately flexed in a seated position, and air is introduced through a cisterna puncture. Unless there is an aqueductal obstruction, such as noted in five patients with obstructing hydrocephalus, air passes into the vallecula and then into the ventricular system as CSF is drained. The passage through which air moves in the sitting position explains why there is a higher incidence of intraventricular air in this position than in the other surgical positions. Air may also enter anteriorly and pass into ventral cisterns and escape into supratentorial regions. The latter, however, is more likely to occur in the lateral (park-bench) or supine position.

Although in the park-bench position the head is only slightly elevated (5–10°), the craniotomy site is dependent (at the base of the skull). By way of an inverted bottle phenomenon (2,3), air passes up to vertex while CSF is lost through the craniotomy. Because the gravitational effect is less, and subsequently a lesser amount of CSF is drained, one should expect a smaller amount of air to be entrapped. Of 40 patients with the surgery performed in the park-bench position, 29 patients had a small amount of intracranial air (73%), and in only three patients was there associated intraventricular air.

In the prone position, the vertex is located lower relative to the operative site than in the other positions. Theoretically, no air can enter the cranium. However, 16 of the 28 patients (57%) with surgery in this position had air demonstrated postoperatively, and four had air in the lateral ventricles. It is interesting to note that all four patients with cervical cord surgery performed in the prone position developed pneumocephalus. It is probable that during surgery the cisterna magnum became filled with air that entered as CSF was removed by surgical suction. When the cisterna magna is filled with air to the lower aspect of the vermis, air may then pass into the vallecula and on into the ventricles (14). If only a small amount of air is trapped in the cisterna magnum, the air may escape to the ventral and to supratentorial subdural areas once the patient is returned to a supine position.

Although we have demonstrated pneumocephalus in a large number of patients, none of the patients developed symptoms of tension pneumocephalus. Several factors have been implicated in the pathogenesis of the aerocele producing tension effect (3,15,16). These are the following: size of volume of intracranial air collection; a functioning V–P shunt; surgical position of patient; N_2O administration; and intraoperative administration of a dehydrating agent. Additionally, in this study we have assessed two other factors: duration of surgery and position of the head in the postoperative period.

The volume of air entrapped intracranially is difficult to quantitate. Monajati et al. (17), assisted by computerized tomography (CT), estimated subdural air to be more than 65 cm^3 in two symptomatic (tension) patients, and less than 20 cm^3 in four asymptomatic patients. They suggested that the size of subdural pneumatoma is an important differential between tension and benign pneumocephalus. Because none of our patients had pneumocephalus evaluated by CT study, in vivo estimation of air volume was difficult though not impossible. In some of our sitting patients with coexisting hydrocephalus, bilateral intraventricular as well as bifrontal subdural air was seen, and it could be reasonably estimated to be more than 65 cm^3. However, none of our 32 patients with large amounts of intracranial air after posterior fossa craniotomies in the sitting position subsequently developed tension effects. Therefore explanation of the etiology of tension by large volume of air alone is not entirely satisfactory.

Continued administration of N_2O after the closure of dura has been theorized to increase intracranial pressure (4,6,7,18–20). The mechanism is thought to be due to expansion of the entrapped air volume. Although this effect is easily explainable intraoperatively, intracranial air that caused tension several hours after N_2O administration had been discontinued is difficult to explain on this basis. Of 77 patients with pneumocephalus, none of the 42 patients given N_2O during surgery developed postoperative neurologic symptoms attributable to pneumocephalus.

Presence of a V–P shunt has been postulated to act as a buffer against development of cranial tension (3). This beneficial effect, however, was not substantiated by our study. The number of patients with V–P shunts was low (group 1, 10/32; group 2, 2/40; group 3, 3/28) relative to incidence of pneumocephalus, and none of those patients became clinically symptomatic (tension pneumocephalus). Furthermore, obstruction of V–P shunt by air bubbles (airlock) may even negate the buffering effect. Presence of V–P shunt, therefore, does not appear to be relevant to the development of cranial tension or the accumulation of intracranial air.

Intraoperative use of dehydrating agents is frequently mentioned as a contributing factor to the development of tension pneumocephalus. The present study did not demonstrate that this factor has an effect on the development of pneumocephalus, except in group 3 patients whose surgery was performed in the prone position. In this position, all cases of pneumocephalus developed in patients who had not received mannitol, and those who had received mannitol did not develop pneumocephalus. This unusual effect can be explained. The patients who had received mannitol have a less than normal amount of CSF and did not lose a significant amount of fluid during surgery.

Two factors are believed to be important in the eventual development of intracranial tension with aerocele. One is duration of surgery and the other is postoperative care. It is possible with longer surgery that a greater amount of CSF is drained and more extensive tissue injury occurs, with consequent formation of greater brain edema. Because of the presence of the aerocele, even a slight increase in volume of other intracranial constituents may increase intracranial pressure, and the aerocele will become symptomatic. The length of surgery was significantly shorter in patients in the present study with pneumocephalus when compared with our four previously reported cases of tension pneumocephalus (8) (Table 4). This may explain in part why none of the patients with pneumocephalus become symptomatic.

We think that the absence of symptoms related to the presence of intracranial air in this study can also be explained by the postoperative care. The change from the head-up to horizontal position may increase ICP if compensatory absorption of CSF is impaired or engorgement of the vascular tree occurs (21). The increase is more likely to occur when a large amount of intracranial air is present. All patients in this study were placed in a 30° head-up position postoperatively. This maneuver may have reduced the intracranial pressure and made pneumocephalus asymptomatic. Recently Durward et al. (22), have shown that a moderate degree of head elevation (15–30°) provides a consistent reduction of ICP in patients with intracranial hypertension.

Finally, the present study has brought up an important clinical issue. Because a high incidence of pneumocephalus is associated with the posterior fossa surgery, the question of whether N_2O administration should continue after the dural closure, or should be given at all, has become critical. In view of the many reported cases of intracranial air behaving as a tension mass during N_2O anesthesia (1,4,16,18,23), it would seem to be prudent to discontinue N_2O administration at least 10 min prior to closure of the dura, the time period required for the assurance of N_2O to be carried away from the aerocele (24). Furthermore, for surgery after posterior fossa craniotomy in these patients, perhaps N_2O should not be administered at all.

In summary, our study has shown that pneumocephalus frequently occurs after posterior fossa or cervical cord surgery, especially performed in the sitting position; postoperative pneumocephalus is usually asymptomatic; a single contributing factor, such as preexisting V–P shunt, use of N_2O, or intraoperative dehydrating agents does not play a solitary direct role in the incidence of postoperative pneumocephalus; and in a patient with coexisting hydrocephalus, when the surgery is performed in sitting position, there is an increased risk of trapping a large amount of intracranial air.

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The Effect of Diazepam on Induction of Anesthesia with Alfentanil

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This study investigated the effect of intravenous diazepam on induction of anesthesia with alfentanil. Forty ASA physical status I and II patients were given one of four treatments: alfentanil 100 μg/kg or 200 μg/kg, without diazepam or preceded by 0.125 mg/kg diazepam intravenously. Blood pressure, heart rate, respiration, response to verbal command, and movement were assessed for 5 min, and blood was taken for measurement of histamine, epinephrine, and norepinephrine. All ten patients receiving 100 μg/kg and five of the ten patients receiving 200 μg/kg of alfentanil responded to voice after 5 min, but only one in each group responded when it was preceded by diazepam. There was no rigidity or serious arrhythmias in any patient. Heart rate increased in patients receiving alfentanil alone. Blood pressure increased in those receiving 100 μg/kg but not 200 μg/kg. In patients given diazepam, tachycardia did not occur, but blood pressure decreased after administration of alfentanil. There were no significant changes in plasma levels of histamine or catecholamines. Five of the six cases of inadequate postoperative ventilation were in patients given diazepam. Despite these effects, diazepam or some other hypnotic agent may be indicated when alfentanil is used for induction.

Key Words: ANALGESICS—alfentanil. ANESTHETICS, INTRAVENOUS—alfentanil, diazepam. HYPNOTICS, BENZODIAZEPINES—diazepam.

Alfentanil is a tetrazole derivative of fentanyl with a more rapid onset but a shorter duration of action and one-third the analgesic potency of fentanyl (1–3). Studies in animals have shown a peak analgesic effect 2–3 min after injection and a duration of action of 10 min at doses twice the ED_{50} analgesic dose. These properties have led to evaluation of alfentanil for induction of anesthesia in healthy patients (4–7) as well as in patients with coronary artery disease (8,9). High doses of alfentanil do produce unconsciousness, although rapid injection of alfentanil may produce hypotension (6). Hypotension has been a particular problem in older patients with cardiovascular disease or treated hypertension.

It has been suggested that benzodiazepine premedication may interact with alfentanil to speed induction, reduce alfentanil dosage requirements, decrease muscle rigidity, and prolong recovery time (4). We have previously shown, however, that diazepam and fentanyl may interact to produce vasodilation and hypotension in patients with coronary artery disease (10). The present study was, therefore, undertaken to determine the effect of intravenous diazepam on the hypnotic and cardiovascular responses to large doses of alfentanil. We studied a wide age range of patients without cardiovascular disease to assess the effect of age on these responses. In addition, plasma histamine and catecholamine levels were measured in an attempt to determine the etiology of observed cardiovascular changes.

Materials and Methods

The study included 40 ASA class I and II patients, 19–75 yr old, without cardiovascular or respiratory disease, who were scheduled for elective surgery of anticipated duration longer than one hour. The patients gave informed written consent at the time of the preoperative visit, and the protocol was approved by the Subcommittee on Human Studies.

No premedication was given. The patients were assigned randomly to one of four groups, each containing 10 patients, which were disclosed to the investigator after patient enrollment in the study. In

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Table 1. Demographics (mean ± SEM)

	Group			
	I	II	III	IV
Age (yr)	43.5 ± 6.0	48.6 ± 5.6	38.9 ± 4.5	40.4 ± 4.4
(Range)	(19–71)	(27–75)	(21–62)	(22–66)
Height (cm)	176.9 ± 2.8	171.8 ± 3.3	176.4 ± 3.3	174.6 ± 2.8
	(159–185)	(156–185)	(159–192)	(154–185)
Weight (kg)	79.9 ± 5.2	70.9 ± 3.6	81.9 ± 5.3	73.2 ± 3.8
	(61–112)	(50–86)	(51–108)	(58–95)
Duration of surgery (min)	168.7 ± 20.8	143.7 ± 37.6	153.1 ± 20.1	216.0 ± 52.2
	(82–254)	(20–440)	(85–283)	(60–592)
Male:female	8:2	7:3	8:2	8:2

group I, 100 μg/kg of alfentanil was used for induction of anesthesia; in group II, diazepam, 0.125 mg/kg plus alfentanil, 100 μg/kg, were used; in group III, anesthesia was induced with alfentanil, 200 μg/kg; and in group IV, diazepam, 0.125 mg/kg plus alfentanil, 200 μg/kg, were given.

On the patient's arrival in the operating room, an intravenous infusion (Ringer's lactate) for drug administration and an 18-gauge Teflon cannula for blood sampling were placed in opposite arms. Blood pressure was measured with a standard Riva Rocci cuff, pulse rate by ECG or radial palpation, and respiratory rate by chest wall observation.

Pancuronium, 0.02 mg/kg, was given intravenously to all patients 5 min after intravenous diazepam, 0.125 mg/kg, was given to patients in groups II and IV. Patients were given 100% O_2 by face mask. The alfentanil dose, diluted in Ringer's lactate solution to a volume of 45 ml, and metocurine, 0.05 mg/kg diluted to a volume of 9 ml in a separate syringe, were then infused concomitantly over 90 sec (alfentanil at a rate of 66.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in groups I and II and 133.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in groups III and IV).

The pancuronium and metocurine doses were selected to produce less than 100% depression of single twitch (11). This allowed us to use somatic responses to assess level of consciousness. Loss of consciousness was assessed by response to verbal command, i.e., asking the patient to open his or her eyes and squeeze the anesthesiologist's hand. Responses were scored quantally (present/absent) every 30 sec during the infusion and 90 sec and 5 min after completion of the alfentanil–metocurine infusion. The 90-sec reading was chosen for comparison with earlier studies (5,6).

When respiration ceased, controlled ventilation using a face mask and 100% O_2 was begun and continued for 5 min. Thiopental, 1 mg/kg, was then given intravenously to ensure patient unconsciousness and tracheal intubation was performed. Additional thiopental was given before intubation if the patient remained responsive to command. Blood pressure and pulse rate were recorded, and venous blood samples were taken before induction, after diazepam (if given), after pancuronium, 2 and 5 min after the administration of alfentanil and metocurine, and 30 sec after intubation.

After tracheal intubation, anesthesia was maintained with 66% N_2O in O_2. No further opioids or sedatives were given. Enflurane was given as needed for maintenance of anesthesia. Supplemental muscle relaxants were given as indicated by monitoring of train-of-four responses. We recorded the presence or absence of truncal rigidity, cough, or laryngospasm during induction. The response to laryngoscopy and intubation was assessed by the position of the vocal cords and presence of tearing or movement after intubation.

At the end of surgery, neuromuscular blockade was reversed with neostigmine, 2.5 mg, and atropine, 1.2 mg, and enflurane was discontinued. The time at which response to command returned was noted. If respirations were less than 10 breaths/min, the anesthesiologist encouraged the patient to breathe, and if this proved inadequate naloxone was given. All patients were extubated in the operating room. Patients were assessed in the recovery room for nausea, vomiting, and need for further analgesia. All patients were seen postoperatively and questioned about recall or unpleasant experiences.

Hemodynamic data and changes in plasma histamine and catecholamine levels were analyzed by two-way analysis of variance for repeated measures (BMDP Statistical Software, UCLA, 1981). Quantal data were analyzed by χ^2 for independent samples.

Catecholamine and Histamine Assays

Each 10-ml sample of blood was drawn into a heparinized tube (Vacutainer, Becton-Dickenson, Rutherford, NJ) and immediately placed on ice. Tubes were then centrifuged at 2000 rpm, 0–5°C for 10 min, and the plasma layer drawn off into polypropylene tubes (Sarstedt #55.526) and stored at −70°C. Plasma histamine levels were measured using the radioenzymatic assay described by Verburg et al. (12), which has a sensitivity of 2 pg/ml. Normal baseline plasma histamine levels in our laboratory are 300 ± 80 pg using this assay—a somewhat lower control value than we have previously described (13). Plasma epinephrine and norepinephrine levels were measured by the radioenzymatic assay of DaPrada and Zucher (14). The normal value for epinephrine is 125 ± 10 pg/ml and for norepinephrine 540 ± 25 pg/ml.

Results

There were no significant differences between the four treatment groups in mean age, weight, height, duration of surgery, and male-to-female ratio (Table 1). Each group contained a few patients at the extremes of our age range.

Most patients rapidly lost consciousness during or shortly after the alfentanil infusion. Five patients ceased responding before the infusion was completed, and all five had received diazepam. All 40 patients became apneic during alfentanil-relaxant administration. Patient responses are listed by groups in Table 2. The number of patients responding to command 90 sec after administration of alfentanil was significantly reduced in patients given diazepam (groups II and IV) compared to patients not receiving diazepam (groups I and III). Doubling the dose of alfentanil from 100 to 200 μg/kg did not significantly decrease the number of patients responding. Seven of the 27 patients who failed to respond to voice at 90 sec regained response by 5 min. At this time, 15 of the 20 patients not receiving diazepam were responsive to command compared to two of the 20 receiving diazepam ($\chi^2 = 17.2$, $P < 0.001$). The presence or absence of response did not bear any consistent relationship to patient age (Fig. 1).

Two patients in group IV had fine muscular twitching for a short period immediately after administration of alfentanil. Two patients (one in group II and one in group IV) had gross limb movement during induction. One of these patients was subsequently found to have a history of significant alcohol consumption. There were no episodes of coughing or laryngospasm at any time in any patient. At laryngoscopy, no patient had adduction of the cords, and there were no technically difficult intubations. The frequency of tearing was low and not significantly different between the four treatment groups.

Table 2. Number of Patients Responding to Verbal Stimulus

	Group			
	I	II	III	IV
Response at 90 sec[a]	6	1	5	1
Response at 5 min[b]	10	2	5	0
Required > 1 mg/kg of thiopental before induction[c]	5	0	1	1
Movement after intubation[d]	9	5	6	2
Tearing after intubation	3	2	1	0

For groups I and III vs groups II and IV: [a]$P < 0.005$; [b]$P < 0.001$; [c]$P < 0.01$; [d]$P < 0.025$.

Cardiovascular responses are summarized in Figure 2. Baseline heart rate values were not significantly different among groups. Heart rate increased in all groups above baseline levels after pancuronium, but the increases were statistically different only in groups III and IV. After alfentanil the pulse rate returned rapidly to baseline in patients given diazepam (groups II and IV). In contrast, pulse rate continued to increase in groups I and III.

Baseline values for mean systemic pressure were not statistically different among groups, although baseline levels in group I were slightly lower. After alfentanil, pressure increased significantly above baseline in group I but not in group III. This was primarily due to the difference in baseline values because after alfentanil was given, blood pressures were similar in both groups. Groups II and IV behaved very differently. Blood pressure decreased sharply after alfentanil and remained depressed until laryngoscopy and intubation. Two patients in group IV had decreases in mean arterial pressure greater than 30% from baseline at 2 min.

The data demonstrate that doubling the dose of alfentanil from 100 μg/kg to 200 μg/kg does not significantly change responses of heart rate or blood pressure to laryngoscopy and tracheal intubation, but that responses to either dose of alfentanil were substantially altered by diazepam pretreatment.

No episodes of bradycardia were observed. Atrial premature contractions were seen in one patient in group I before intubation and in one patient in group II immediately after intubation. Both arrhythmias resolved spontaneously. One patient in group IV had a transient nodal rhythm after alfentanil that resolved before intubation.

There were no significant changes in plasma histamine levels at any time in any group (Fig. 3). No cutaneous signs of histamine release such as redness or urticaria were observed. The baseline values of

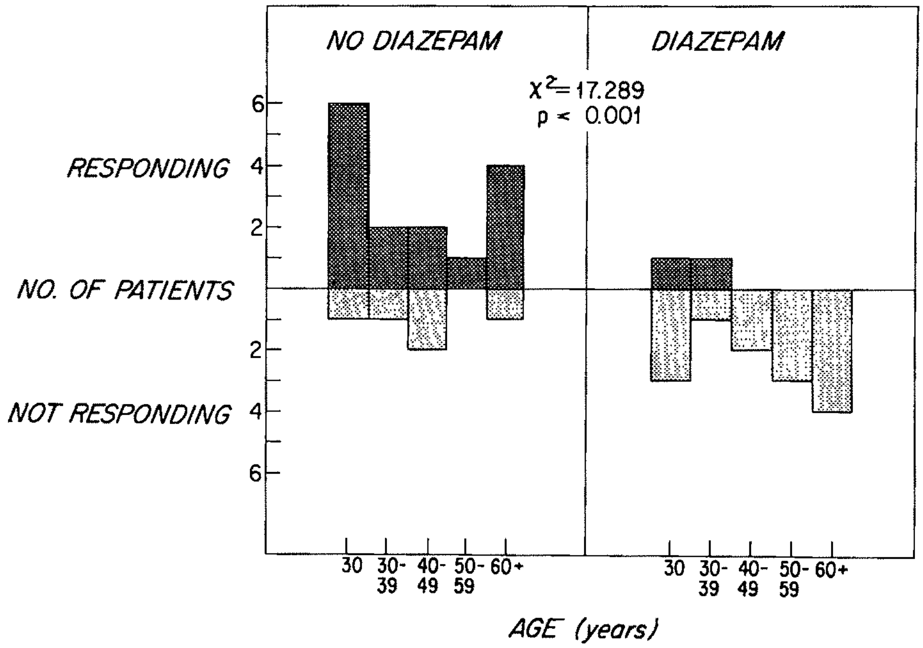

Figure 1. Numbers of patients responding or not responding to command 5 min after completion of alfentanil infusion. Administration of diazepam significantly decreased the frequency of response, whereas age had no effect.

norepinephrine were high in these unpremedicated patients and remained elevated throughout induction, but there were no statistically significant inter- or intragroup differences in the level of either norepinephrine or epinephrine (Fig. 3).

Thirty-eight patients required enflurane for maintenance of anesthesia. Two patients (one in group II and one in group III) did not require additional inhalation anesthesia for procedures that lasted 1.5 and 2 hr, respectively. The time elapsed between alfentanil administration and the introduction of enflurane ranged from 5 min to 120 min, and there was no significant difference between groups.

Patients experiencing postoperative respiratory depression are described in Table 3. Two patients in group II, one in group III, and two in group IV had slow respiratory rates (<10 breaths/min) on awakening, but increased their ventilation in response to command and they were not given naloxone. Another patient in group IV remained apneic and nonresponsive 10 min after completion of surgery (1 hr 48 min after the start of anesthesia) and responded well to 0.1 mg naloxone intravenously. Five of these six cases occurred in patients receiving diazepam, and these cases were of shorter duration than the average for each group. One case of respiratory depression occurred in a 33-yr-old patient who had not received diazepam (group III) and whose anesthesia lasted 3 hr 22 min. There was no apparent relationship between age and the occurrence of respiratory depression.

The overall incidence of nausea and vomiting was 30%; there was no significant difference among the four groups. Two patients had recall for events during induction. Neither patient had received diazepam, and both were responsive at 5 min after alfentanil. No patient remembered intubation or had recall of any intraoperative events.

Discussion

Although several studies have described the use of alfentanil in high doses to induce anesthesia, there has been no controlled study to assess the effect of diazepam on the efficacy of this agent. As might have been predicted, prior administration of diazepam greatly increased the hypnotic effect of alfentanil. Our results show that diazepam plus alfentanil is more effective in producing unconsciousness than alfentanil alone. In fact, alfentanil administered at the rates of doses used in this study appears to be inadequate to produce sleep without the addition of another hypnotic agent. This appears to hold true even for patients 60-yr and older. Similar results have recently been reported for fentanyl when moderate doses (30 μg/kg) are used for induction (15). Although the number of patients studied does not allow us to conclude that age does not influence response to alfentanil, it is clear that older individuals may remain conscious after these induction doses.

We chose to administer alfentanil over 90 sec because of reports of hypotension at fast rates of injection (6). At these rates of injection (66.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 133.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) blood pressure did not de-

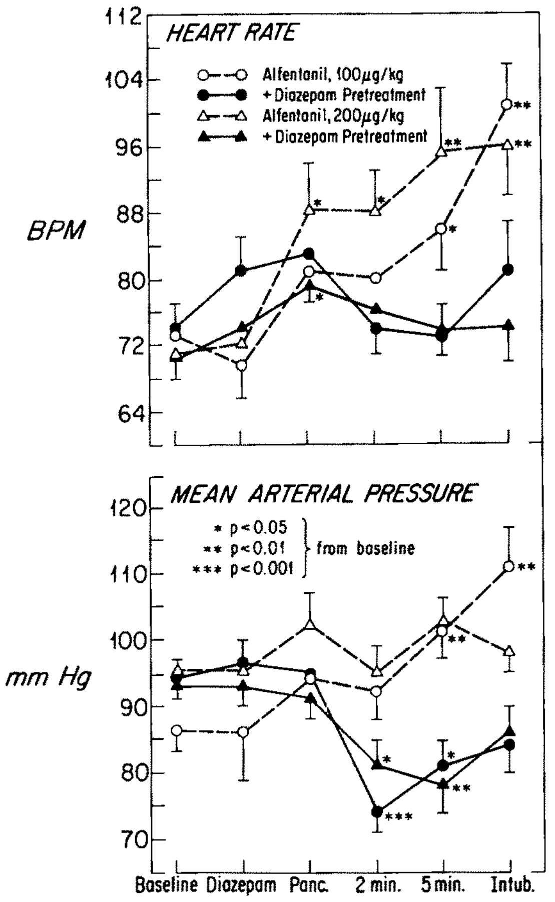

Figure 2. Hemodynamic measurements during induction. Bars denote SEM. See text for details.

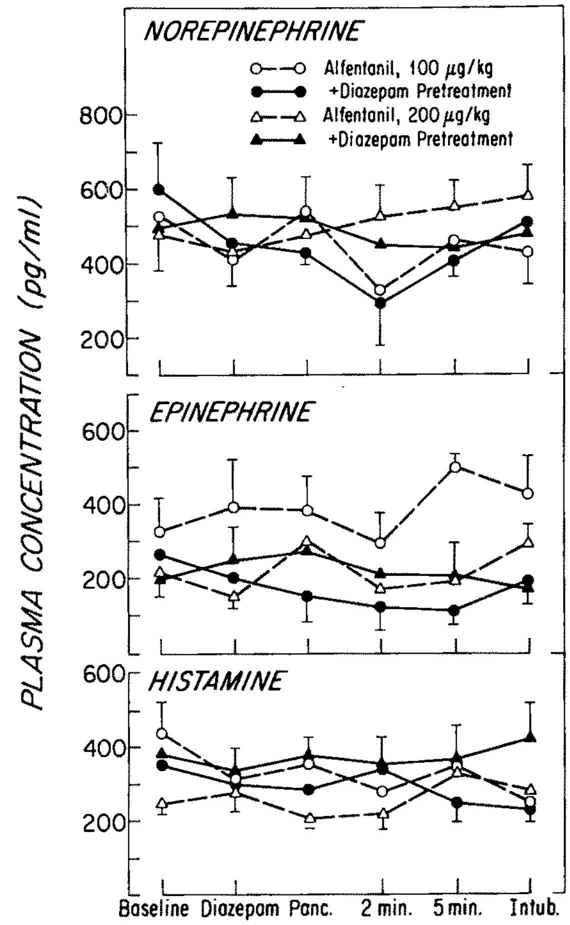

Figure 3. Plasma concentrations of catecholamines and histamine during induction. Bars denote SEM. No significant changes were observed at any time in any group.

crease in groups I and III, but 55% of these patients were still responsive at 90 sec. Our results are at variance with previous studies. McDonnell et al. (5) found the ED_{90} for loss of response to voice to be 111 µg/kg; however, he used much faster rates of injection (600–1800 $\mu g \cdot kg^{-1} \cdot min^{-1}$). We can find no explanation for the dose of 119 ± 20 µg/kg reported by Nauta et al. (4) required to produce loss of consciousness when the drug was injected at a much slower rate of 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Our findings also suggest that the hypnotic effect of alfentanil is only brief in duration: in group I, four of 10 patients lost, then regained consciousness prior to intubation. Alfentanil pharmacokinetics have been well described (16–20). This lipophilic drug has a redistribution half-life of 11.6 min and a somewhat slower rate of elimination (17). When alfentanil is used in the manner described in this study, termination of the hypnotic effect occurs just as it does with thiopental (redistribution half-life 3.3 min (21)): brain concentration decreases rapidly to subhypnotic levels, while a good deal of active drug remains in blood and peripheral tissues. Although 100 µg/kg of alfentanil produces less than 5 min of hypnosis, blood and CNS concentrations sufficient to produce analgesia and respiratory depression persist for a considerably longer time.

It is well established that opioid-induced respiratory depression is potentiated by the occurrence of sleep (22). Hypnotic agents such as diazepam or enflurane interact with opioids to increase both intra- and postoperative respiratory depression. In our study, clinically significant respiratory depression was more frequent in patients who had been given diazepam; however, all these patients responded to simple treatment. Neither age, alfentanil dose, nor duration of operation were reliable predictors of postoperative respiratory depression. The use of enflurane (a respiratory depressant as well as hypnotic) complicates the interpretation of these results, but one patient with respiratory depression did not receive enflurane.

Tomichek et al. (10) found that 0.125–0.5 mg/kg of diazepam followed by 50 µg/kg of fentanyl decreased systemic vascular resistance and caused significant

Table 3. Postoperative Respiratory Depression

	Group			
	I	II	III	IV
Number with respiratory depression	0	2	1	3
Ages (yr)	—	33, 75	33	38, 53, 66
Duration of anesthesia in patients with respiratory depression (hr)	—	1.4 ± 0[a]	3.4	1.9 ± 0.4[a]
Duration of anesthesia in patients without respiratory depression (hr)	—	3.2 ± 0.7	2.6 ± 0.3	4.8 ± 1.1

[a] Duration of anesthesia in patients with respiratory depression was significantly shorter ($P < 0.001$) than in patients in the same group without respiratory depression.

hypotension. These changes were not seen with fentanyl alone. It seems likely that the decreases in pressure seen in our study were due to a similar mechanism. The peripheral vasodilation is clearly not due to histamine release. Alfentanil may produce a decrease in brainstem sympathetic output such as that described for morphine (23). One would expect other CNS depressants to potentiate this effect, although premedication with oral lorazepam does not appear to produce this interaction with alfentanil in cardiac surgical patients (9).

There was no evidence of vagally mediated bradycardia in our patients, but all had received pancuronium. The increase in heart rates seen in all our groups initially was probably due to the vagolytic effect of the relaxant because there was no evidence of catecholamine release. Diazepam appeared to limit this effect on heart rate.

Chest wall rigidity occurs in as much as 75% of unpremedicated patients when alfentanil is used as an induction agent (5). We chose a combination of pancuronium, 0.02 mg/kg, and metocurine, 0.05 mg/kg, to prevent rigidity and to facilitate intubation. The doses of relaxants were deliberately selected to be below the ED_{95} for suppression of single twitch (11). This allowed the patient to respond to voice and indicate consciousness up to 5 min, as described. Metocurine and pancuronium in these doses did not release histamine or increase plasma levels of catecholamines. The combination was sufficient to prevent rigidity in all cases.

In summary, 100–200 μg/kg of alfentanil injected over 90 sec does not reliably produce sleep in healthy unpremedicated patients. More rapid administration of the opioid (as in previous studies) or concomitant treatment with diazepam will produce acceptable hypnosis but may also produce hypotension. Patients with marginal cardiovascular reserve seem to be the ones most likely to benefit from this sort of high-dose opioid induction, but the occurrence of hypotension may limit use of the technique in such individuals. On the other hand, there were several advantages from these large doses of analgesic: there was total absence of cough, laryngospasm, or hiccough during induction; there was relatively little autonomic response to laryngoscopy and tracheal intubation (the somatic responses would probably have been supressed by an adequate dose of relaxant); and these benefits were obtained without the need for prolonged postoperative ventilation.

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Hemodynamic Changes after the Administration of Protamine

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CASTHELY PA, GOODMAN K, FYMAN PN, ABRAMS LM, AARON D. Hemodynamic changes after the administration of protamine. Anesth Analg 1986;65:78–80.

Hemodynamic changes associated with the administration of protamine were studied in 30 dogs divided into three equal groups. Protamine (1 $mg \cdot kg^{-1} \cdot min^{-1}$ for 4 min) was administered 10 min after 4 $mg \cdot hg^{-1}$ heparin was given via a left atrial (LA) line in group A, via a central vein in group B, and via a peripheral vein in group C. Protamine given through the central venous pressure (CVP) line resulted in an immediate and significant decrease in mean arterial pressure (MAP) to 60 ± 4.5 mm Hg ($P < 0.025$) from 72 ± 7 mm Hg immediately after the protamine and to 58 ± 5 mm Hg ($P < 0.025$) 5 min later and with an increase in cardiac index (CI) to 3.7 ± 0.3 $L \cdot min^{-1} \cdot m^{-2}$ from 2.8 ± .25 $L \cdot min^{-1} \cdot m^{-2}$ immediately after the protamine ($P < 0.005$), followed by a decrease back to 2.7 ± 0.3 $L \cdot min^{-1} \cdot m^{-2}$ 5 min later. Mean arterial pressure and CI remained unchanged after administration of protamine via the peripheral vein or the left atrium. Systemic vascular resistance (SVR) decreased significantly only after administration of protamine via the CVP and was statistically unchanged when administered via the peripheral and LA line. Plasma histamine levels increased significantly after administration of protamine through the central line but remained unchanged after administration via a peripheral vein or the left atrium. We conclude that hemodynamic changes after protamine administration may be related to protamine-induced histamine release from the lung and are greatly influenced by the site of administration. The greatest hemodynamic effect occurred when protamine was administered via the right atrium and the least when administrated via the peripheral vein. This is probably due to the fact that protamine, when injected into the right atrium, forms protamine heparin complex, which goes to the lung to release histamine, whereas it becomes diluted before reaching the lung when injected into a peripheral vein or left atrium.

Key Words: BLOOD, COAGULATION—protamine.

Administration of protamine after cardiopulmonary bypass has been said to be associated with significant decreases in cardiac output and arterial blood pressure (1). However, a recent report has shown no hemodynamic changes after administration of protamine (2). The present study was undertaken to compare hemodynamic changes in dogs with good ventricular function after administration of protamine via the left atrium (group A), the right atrium (group B), or a peripheral vein (group C).

Methods

Thirty mongrel dogs weighing 18–20 kg were divided into three equal groups: group A, dogs given protamine via a left atrial catheter; group B, those given protamine via a central venous catheter; and group C, given protamine via a peripheral vein. Protamine dosage (4 mg/kg) was the same and was preceded by 4 mg/kg heparin for 10 min in all dogs. They were anesthetized with pentobarbital, 20 mg/kg, intubated with a #10 Rusch tube, and paralyzed using 0.025 mg/kg pancuronium to produce immobilization. Dogs were mechanically ventilated, using a tidal volume sufficient to maintain a Pa_{CO_2} within normal limits. Anesthesia was maintained with 60% N_2O in 40% oxygen.

The left femoral artery was cannulated for arterial pressure monitoring. A #7 French thermodilution pulmonary artery catheter was inserted through a femoral vein into the pulmonary artery for calculation of cardiac output (CO), measurement of pulmonary vascular pressures and for sampling of mixed venous blood. Standard formulae were used to calculate systemic and pulmonary vascular resistance.

Cardiac output was determined in triplicate with 95% reproducibility by using an Edwards Computer Model #9520A. Through a small left thoracotomy performed in the 6th intercostal space, a 60-cm 14-gauge

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Table 1. Cardiovascular Changes after Protamine Administration

	Group	Baseline	Immediately after protamine	5 min after protamine
ACT	A	480 ± 10.5	120 ± 7	125 ± 7.5
	B	490 ± 11.0	115 ± 7.5	110 ± 7.5
	C	495 ± 15.0	104 ± 8.5	105 ± 7.5
Histamine[a] (ng/ml)	A	1.5 ± 0.8	2.75 ± 1	3.1 ± 1.2
	B	1.85 ± 0.75	8.5 ± 0.95[b,c]	8.6 ± 1.2[b,c]
	C	1.90 ± 0.85	2.90 ± 1.2	2.85 ± 1.05
Heart rate (beats/min)	A	95 ± 7	92 ± 8	96 ± 7.5
	B	90 ± 6.5	92 ± 5	93 ± 6
	C	92 ± 6	94 ± 4.5	91 ± 5
Mean arterial pressure (mm Hg)	A	70 ± 7	68 ± 6	71 ± 7.5
	B	72 ± 7	60 ± 4.5[b,c]	58 ± 5[b,c]
	C	75 ± 8.5	70 ± 76	9.5 ± 7.2
Pulmonary artery pressure (mm Hg)	A	18 ± 1.5	17.5 ± 21	8.5 ± 1.5
	B	16.5 ± 1	30.5 ± 0.5[b]	25.75 ± 0.40[b]
	C	17.75 ± 1	17.5 ± 1.5	13 ± 1.20
Wedge (mm Hg)	A	6 ± 0.5	4 ± 0.4	4.5 ± 0.4
	B	2 ± 0.6	1.5 ± 0.5	7 ± 0.6[b,c]
	C	1.25 ± 0.4	2 ± 0.5	2.75 ± 0.2
Right arterial pressure (mm Hg)	A	7 ± 0.5	6 ± 0.4	5 ± 0.5
	B	8 ± 0.6	11 ± 0.1[b,c]	4 ± 0.15
	C	7.5 ± 0.5	7 ± 0.6	7.5 ± 0.5
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	A	2.7 ± 0.2	2.8 ± 0.25	2.75 ± 0.3
	B	2.8 ± 0.25	3.70 ± 0.3[b,c]	2.70 ± 0.3
	C	2.75 ± 0.3	2.8 ± 0.35	2.9 ± 0.4
Systemic vascular resistance (units)	A	25.5 ± 2	22.14 ± 1.9	24 ± 2.2
	B	26 ± 2.5	15.40 ± 1[b,c]	20 ± 1.25[b,c]
	C	24.5 ± 2.4	22.5 ± 2.5	21.37 ± 2.15
Pulmonary vascular resistance (units)	A	5.7 ± 0.5	4.70 ± 0.5	5.2 ± 0.45
	B	5.9 ± 0.6	10.05 ± 0.1[b,c]	8.07 ± 0.30[b,c]
	C	6 ± 0.55	5.60 ± 0.3	5.40 ± 0.4

[a] Group A, LA; group B, CVP; group C, peripheral vein.
[b] $P < 0.05$ significant within each group.
[c] Significant between groups.

catheter was inserted via the superior pulmonary vein into the left atrium.

All pressures were measured and recorded using nine Hewlett Packard Transducers with a six-channel recorder, which were calibrated by a mercury manometer and recalibrated every hour.

Baseline data were measured 5 min before protamine infusion, immediately after administration, and 5 min later. Plasma histamine concentrations were determined using a radioenzymatic assay (3).

Statistical analysis was performed within each group using Student's *t*-test for paired data. Values were expressed in mean ± standard error of the mean, and $P < 0.05$ was considered statistically significant. Statistical significance between groups was done using multivariant analysis (LSD procedure).

Results

Protamine given through the central venous pressure (CVP) line resulted in an immediate and significant decrease in mean arterial pressure (MAP) to 60 ± 4.5 mm Hg ($P < 0.025$) from 72 ± 7 mm Hg immediately after the protamine and to 58 ± 5 mm Hg ($P < .025$) 5 min later, and with an increase in cardiac index (CI) to 3.7 ± 0.3 $L \cdot min^{-1} \cdot m^{-2}$ from 2.8 ± 0.25 $L \cdot min^{-1} \cdot m^{-2}$ immediately after the protamine ($P < 0.005$), followed by a decrease back to 2.7 ± 0.3 $L \cdot min^{-1} \cdot m^{-2}$ 5 min later. Mean arterial pressure and CI remained unchanged after administration of protamine via the peripheral vein or the left atrium. Systemic vascular resistance (SVR) decreased significantly only after administration of protamine via the CVP and was statistically unchanged when administered via the peripheral and left atrial (LA) line. Plasma histamine levels increased significantly after administration of protamine through the central line but remained unchanged after administration through a peripheral vein or the left atrium. No statistically significant changes occurred in activated clotting time (ACT) among the three groups studied.

Discussion

Our data demonstrate that severe hemodynamic changes were associated with significant increases in histamine levels when protamine was administrated via a central venous line. The cardiovascular alterations consisted of hypotension, a decrease in SVR, an increase in PVR, and an increase in cardiac index which returned toward normal a few minutes later. Those changes are compatible with previous studies on the cardiovascular effects of protamine (4,5). When protamine was administered via the peripheral vein or left atrium, the cardiovascular changes were minimal.

Bradycardia, though reported by others, was not observed in our patients. Previous studies have suggested that protamine may have a direct myocardial depressant effect (6,7). Recent studies, however, have demonstrated the absence of myocardial depression after protamine (2). We did not measure *dp/dt* in our dogs. Because the filling pressure was not significantly altered, we assume that the observed hemodynamic changes were probably due to venous pooling and not to myocardial depression.

The hemodynamic changes found in our studies are consistent with protamine-induced histamine release. It has been demonstrated that high levels of protamine will cause mast cells and basophils to degranulate and release histamine more than lower levels of protamine (8).

A possible explanation for the different cardiovascular changes after protamine administration depending upon the route of administration is that the protamine–heparin complex formed when protamine is injected into a peripheral vein or the left atrium is diluted before it reaches the lungs, which are a major site of storage of many vasoactive substances, including histamine. Similar changes do not occur when protamine is injected into a central vein. It is known that protamine acts as a substrate of C reactive protein (CRP), a potent activator of the complement system at the level of C1 (9). This in turn would lead to a C3a, C5a anaphylatoxin generation. Furthermore, heparin and protamine in fresh human serum (9), in amounts lower than those required for complement depletion, have been shown to induce virtually complete depletion of total hemolytic complement via the classical pathway by interaction with the first component of complement (10). In group B animals in the present study, the pulmonary circulation was exposed to a blood concentration of protamine greater than that in the other two groups because of direct administration into the right atrium. The lack of hemodynamic changes when protamine was injected through a peripheral vein or LA line is most likely due to a dilutional effect. Most of the protamine had already been involved in heparin reversal and less reached the lungs to degranulate mast cells and basophils and thus to release histamine. Therefore, the nonimmunologic anaphylactoid reaction frequently seen after the administration of protamine does not occur or occurs minimally after protamine is injected into the left atrium or a peripheral vein. When injected through the CVP catheter, however, the increase of histamine was the highest, suggesting intense complement activation and anaphylactoid reaction. Heparin was adequately reversed independently of the protamine administration because there was no statistical difference in ACT in the three groups.

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Influence of Diltiazem on Cardiovascular Function and Coronary Hemodynamics during Isoflurane Anesthesia in the Dog:

Correlation with Plasma Diltiazem Levels

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KAPUR PA, CAMPOS JH, TIPPIT SE. Influence of diltiazem on cardiovascular function and coronary hemodynamics during isoflurane anesthesia in the dog: correlation with plasma diltiazem levels. Anesth Analg 1986;65:81–7.

Diltiazem was administered to dogs by intravenous infusion to achieve plasma levels of 47 ± 3 (n = 7), 148 ± 12 (n = 8), 263 ± 10 (n = 3), and 379 ± 43 (n = 8) ng·ml^{-1}, to evaluate the effects of diltiazem on cardiovascular function and coronary hemodynamics, when given in the presence of anesthetic concentrations of isoflurane. Plasma level related prolongation of the PR interval of the electrocardiogram was the most prominent effect observed, with development of 2° heart block or junctional rhythms in several of the animals at the two higher plasma levels. Mean arterial pressure, transiently decreased after the loading dose in all groups, was no different from control values after 30 min of infusion. Left ventricular dP/dt was mildly decreased at the three highest plasma levels, whereas right and left heart filling pressures were increased at the two highest plasma levels. Cardiac index and systemic vascular resistance were unchanged. No changes were observed in coronary sinus blood flow, coronary vascular resistance, myocardial oxygen uptake, myocardial lactate extraction, or circulating epinephrine or norepinephrine levels in any of the groups. In the presence of anesthetic concentrations of isoflurane, over the range of plasma levels investigated in this study, the vasodilating properties of diltiazem were not observed, yet conduction effects were prominent and decreases in left ventricular performance occurred. No untoward effects on global myocardial metabolism were detected under these conditions.

Key Words: ANESTHETICS, VOLATILE—isoflurane. HEART—coronary blood flow, myocardial function. IONS—calcium. PHARMACOLOGY—diltiazem.

Diltiazem is similar to verapamil in its mechanism of action to alter the recovery of slow calcium channels from the inactivated state (1). It has been shown to have antiarrhythmic properties (2–4); to alter the amount and distribution of coronary blood flow (5–10); to reduce myocardial oxygen consumption (6), and to enhance myocardial preservation during periods of ischemia (11,12). It is effective in the treatment of both coronary vasospasm and angina pectoris resulting from fixed obstructive coronary artery lesions (13,14), and has been studied as a component in cardioplegia solutions (15).

High plasma levels of diltiazem are usually required to decrease systemic blood pressure in normal subjects (16–18). Kates et al. (19) reported that in halothane-anesthetized swine, a plasma diltiazem level of 1651 ± 139 ng·ml^{-1} achieved by continuous infusion was required to produce a 30% decrease in mean arterial pressure. This plasma level also resulted in a 50% decrease in left ventricular *dP/dt* and cardiac output, a 40% increase in pulmonary artery occluded pressure, and a 60% prolongation of the PR interval, without a significant change in systemic vascular resistance.

The plasma levels of diltiazem investigated in the study by Kates et al., however, were higher than clinically relevant plasma levels of 100–200 ng·ml^{-1}. Information is lacking regarding the hemodynamic effects of lower plasma levels of diltiazem in the presence of inhalation anesthetics. In addition, it is unknown whether diltiazem in combination with inhalation anesthetics may unduly compromise the balance between myocardial oxygen requirements and myocardial oxygen supply.

The present study was designed to include a range of lower plasma levels of diltiazem in an instrumented

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canine model to investigate the plasma level related effects of diltiazem on cardiovascular function and coronary hemodynamics in the presence of isoflurane anesthesia. Isoflurane was studied because of its reported profound effects as a coronary and peripheral vasodilator (20), with the potential for additive effects with diltiazem in this regard.

Methods

Thirteen conditioned mongrel dogs of either sex weighing 23 ± 1 kg (mean ± SEM) with chronic tracheostomies (21) to facilitate an inhalation anesthetic induction were used for fifteen experiments. Anesthesia consisted of isoflurane (1.49–1.54% end tidal concentration) in 40% oxygen in air through a cuffed tracheostomy tube. Ventilation was controlled to maintain normocarbia. Temperature was maintained between 38–39°C with a warming blanket and a heat lamp. The external jugular vein was cannulated for drug administration and infusion of 0.9% NaCl at 5 $ml{\cdot}kg^{-1}{\cdot}hr^{-1}$. A femoral arterial cannula was inserted for obtaining blood samples and for measurement of phasic and mean arterial blood pressure (MAP). A balloon-tipped, flow-directed catheter was positioned in a pulmonary artery via a femoral vein for measurement of right atrial (RA) and pulmonary artery occluded (PAO) pressures and for sampling of mixed venous blood. A micromanometer-tipped catheter (Millar Instruments, Inc.) was positioned in the left ventricle (LV) from a femoral artery for measurement of LV pressure and electronic derivation of LV dP/dt. A 7F woven Dacron coronary sinus thermodilution catheter (model CCS-7U-90B, Webster Laboratories, Inc., PO Box 237, Altadena, CA) was passed into the coronary sinus under fluoroscopic control via an external jugular vein to measure coronary sinus (CS) pressures and blood flow and to obtain CS blood samples. Its position was confirmed every 30 min by injection of a small amount of contrast dye (Renografin) to outline the sinus. Further confirmation of correct position of the CS catheter was obtained by observing CS pressure wave form and by measurements of coronary sinus P_{O_2}. Coronary sinus blood flow was measured in duplicate using the technique of Ganz et al. (22) and the formula $\dot{Q}_{CS} = [(T_B - T_I/T_B - T_M) - 1]$ (26.448), where $\dot{Q}_{CS}$ is the CS blood flow in $ml{\cdot}min^{-1}$ and T represents the temperatures in °C of blood (B) injected indicator (I), and the mixed (M) indicator and blood. The number 26.448 is a constant factor relating to the specific heat and density of blood and of the saline indicator when injected at a rate of 24 $ml{\cdot}min^{-1}$.

Heart rate (HR), MAP, RA, PA, CS, and LV pressures, and LV dP/dt were recorded continuously. In addition, the ECG was intermittently recorded at fast paper speed (100 $mm{\cdot}sec^{-1}$) for measurement of PR intervals. Inhaled and exhaled gases were analyzed by a mass spectrometer (model MGA-1100, Perkin-Elmer Corp., Pomona, CA). Exhaled gas volume was measured with a modified electronic volume displacement spirometer (model 220, Cardiopulmonary Instruments, Inc., Houston, TX). Computations of whole body oxygen uptake ($\dot{V}O_2$) were performed in real time at approximately 1-min intervals using a general purpose laboratory minicomputer (Data General Corp., Framingham, MA) (23) and the formula $\dot{V}O_2 = V_E\{[F_{I_{O_2}} (F_{E_{N_2}}/F_{I_{N_2}})] - F_{E_{O_2}}\}$, where V_E is the expired volume and F_E and F_I are the expired and inspired fractions of the specific gases. Intermittent samples were simultaneously taken of arterial, mixed venous, and CS blood. Blood gas tensions and pH were measured with an Instrumentation Laboratories model 813 analyzer. Blood oxygen content was measured with a LEX O_2 Con-TL (Lexington Instruments Corp, Waltham, MA). Cardiac output was determined by the Fick method. Systemic vascular resistance (SVR), coronary vascular resistance (CVR), and cardiac index (CI) were calculated. Myocardial oxygen uptake ($M\dot{V}O_2$) was calculated as the product of arterial minus CS oxygen content (in volumes %), divided by 100, and multiplied by CS blood flow.

Plasma arterial and CS diltiazem and catecholamine levels were assayed by high performance liquid chromatography (24,25). Plasma lactate levels were measured in terms of the generation of NADH spectrophotometrically at 340 nm using the enzyme lactic dehydrogenase as the catalyst. Myocardial lactate extraction ratio (MLE) was calculated as the product of arterial minus CS lactate levels, divided by the arterial lactate level, and multiplied by 100. Serum levels of electrolytes (Na^+, K^+, Cl^-), glucose, and ionized calcium levels were measured using an automated analyzer (Beckman Instruments).

Diltiazem was freshly prepared in 0.9% NaCl in a concentration of 0.5 $mg{\cdot}ml^{-1}$. To produce a clinically relevant range of plasma diltiazem levels, four intravenous loading dose and infusion combinations were chosen: *a*) 100 $\mu g{\cdot}kg^{-1}$ + 4 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$; *b*) 200 $\mu g{\cdot}kg^{-1}$ + 8 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$; *c*) 300 $\mu g{\cdot}kg^{-1}$ + 12 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$; *d*) 400 $\mu g{\cdot}kg^{-1}$ + 20 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$. After 2 hr stabilization under isoflurane anesthesia, control blood samples and hemodynamic measurements were made. Each experiment then consisted of either dose *a* followed by dose *d*, or dose *b* followed by dose *c*. The loading dose was given over 5 min; and the infusion continued for 30 min, at which time the second loading dose was given in a like manner and the infusion rate increased. Differences in drug

Table 1. Plasma Diltiazem Levels in Arterial (A) and Coronary Sinus (CS) Blood

Group		n	Diltiazem (ng·ml^{-1})[a] Control[b]	5 min	20 min	30 min
I	A	7	0	93 ± 11	47 ± 4	47 ± 3
	CS	5	0	42 ± 3[c]	44 ± 4	51 ± 1
II	A	8	0	184 ± 26	130 ± 11	148 ± 12
	CS	6	0	121 ± 19[c]	123 ± 15	135 ± 15[c]
III	A	8	87 ± 16	443 ± 57	256 ± 15	263 ± 10
	CS	6	70 ± 13	273 ± 24[c]	250 ± 18[c]	252 ± 18
IV	A	8	138 ± 30	617 ± 67	412 ± 40	379 ± 43
	CS	6	152 ± 28	461 ± 50	393 ± 43	443 ± 72

[a] Mean ± SEM.
[b] For groups III and IV, diltiazem present in plasma at control because the higher plasma levels resulted from the later infusion rates (see methods).
[c] $P < 0.05$ compared to arterial levels for the same dogs by paired t-test.

Table 2. Changes in PR Interval after Diltiazem

Group	n	PR Interval (msec)[a] Control	30 min	90 min after III/IV
I	7	104 ± 6	114 ± 7[c]	—
II	8	102 ± 5	125 ± 10[c]	—
III	8	113 ± 7[b]	143 ± 24[d]	111 ± 15
IV	8	128 ± 9[b]	156 ± 10[d]	119 ± 8

[a] Mean ± SEM.
[b] Diltiazem present at control for groups III and IV (see Table 1).
[c] $P < 0.05$ compared to control.
[d] Mean value for animals remaining in sinus rhythm (see text).

disposition among the animals were anticipated, and it was planned that the experimental results would be analyzed not as a function of dose, but as a function of plasma diltiazem level. The two dogs that were studied twice received the alternate pair of diltiazem doses during the second experiment, which was separated from the first by at least one week. In one of the other animals only one dose of diltiazem could be given because of technical difficulties. Two animals received dose *c* between doses *a* and *d*. The mean total dose of diltiazem for the 15 experiments was 1.55 ± 0.13 mg·kg^{-1} per experiment.

Cardiovascular measurements and samples for measurement of plasma levels of diltiazem, epinephrine, and norepinephrine were taken after the loading doses and at 20 and 30 min of each infusion. The 30-min values from the first infusion rate served as control measurements for the second infusion. Measurements were also made 15, 30, 60, and 90 min after stopping the last infusion in each experiment. Blood losses were replaced with crossmatched heparinized donor dog blood.

Analysis of variance for repeated measures with Bonferroni t-tests was used to evaluate statistical significance of the data. A paired t-test was used to compare arterial and CS diltiazem levels for each group. Regression equations with calculations of correlation coefficients were used to evaluate correlations between variables. A P value of less than 0.05 was considered significant.

Results

Normal levels of arterial pH, PaO_2, PaCO_2, hematocrit, and temperature were maintained throughout the study. There were no significant changes in serum levels of electrolytes, ionized calcium, or glucose. Overlap of plasma diltiazem levels did occur among the infusion rates for different animals, and therefore, results were sorted into four groups by 30-min plasma diltiazem levels: group I, 32–58 ng·ml^{-1} ($n = 7$); group II, 90–190 ng·ml^{-1} ($n = 8$); group III, 230–300 ng·ml^{-1} ($n = 8$); and group IV, 320–601 ng·ml^{-1} ($n = 8$). Mean plasma arterial and CS diltiazem levels for the various measurement periods are given in Table 1. There were no statistically significant differences in the mean 20- and 30-min values during the infusions for any of the variables in any of the four groups. Therefore, 30-min values are used in the figure and tables.

Mean PR intervals are shown in Table 2, at control and 30 min for all four groups, and 90 min after completing the last diltiazem infusion in groups III and IV. The atrioventricular conduction time was prolonged as plasma diltiazem levels increased. Similar diltiazem levels were associated with similar PR intervals. When the regression equation for the plot of diltiazem level vs PR interval was calculated for control and 30-min values, the correlation coefficient was 0.55, with a P value of less than 0.001 ($n = 59$).

Figure 1 shows the values for hemodynamic variables at control, at 30 min for each of the four plasma diltiazem levels, and at 90 min after turning off the highest infusion rate. In contrast to the dose-related conduction interference observed with diltiazem, no significant changes from control were observed in MAP, CI, or SVR after 30 min of infusion at these four plasma

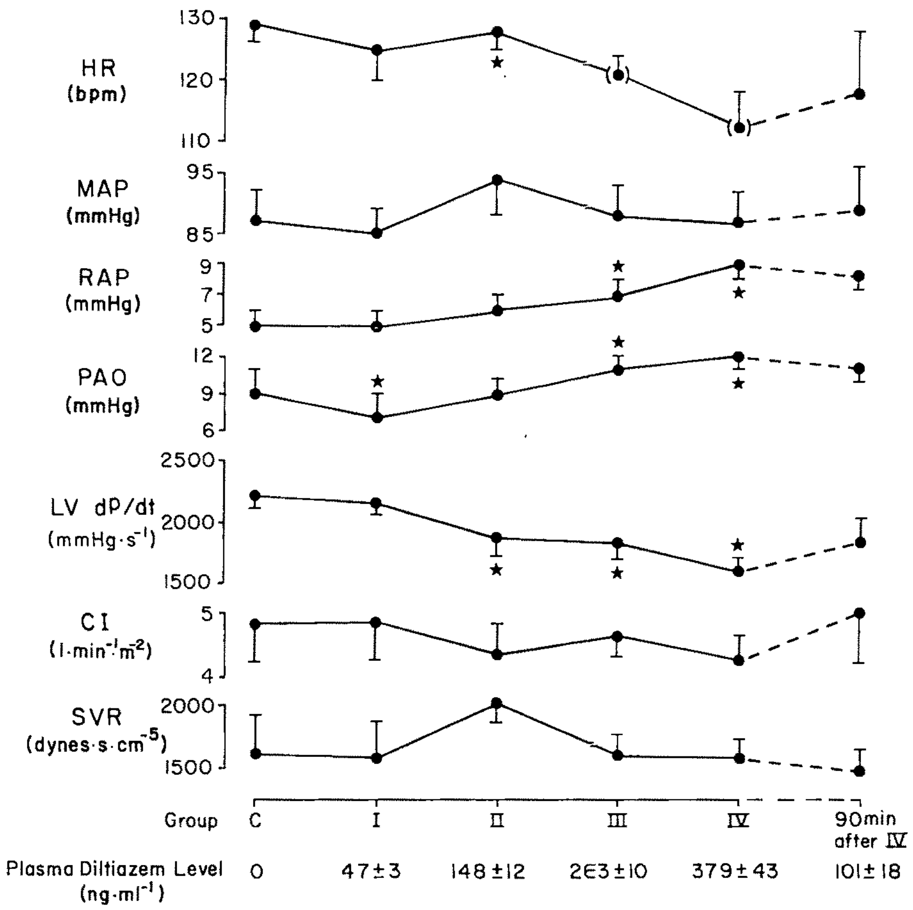

Figure 1. Plot of 30-min values (mean ± SEM) for cardiovascular variables with each level of plasma diltiazem and 90 min after stopping the infusion in group IV. Abbreviations: C, control values for group I; *, $P < 0.05$ compared to control for that group; (●), value for mean heart rate of those animals still remaining in sinus rhythm (see text).

levels, despite increases in filling pressures at the highest two levels and decreases in LV *dP/dt* at all but the lowest plasma level. MAP was significantly reduced, although only transiently, immediately after the loading dose (5-min measurement) in all groups. One animal in group III and three animals in group IV developed Wenckebach 2° heart block; one animal in each of groups III and IV developed a junctional escape rhythm. No significant changes were observed in circulating epinephrine or norepinephrine levels (Table 3).

Control and 30-min values for the four plasma level groups for $\dot{Q}_{CS}$, CVR, MLE, and $M\dot{V}O_2$ are given in Table 4. There were no changes from control values for these variables, nor for $\dot{V}O_2$ (data not presented), in any of the groups when diltiazem was administered in this study in the presence of approximately 1.5% isoflurane (end-tidal).

Discussion

In the presence of 1.5% end-tidal isoflurane anesthesia in this study, plasma levels of diltiazem at which prolongation of atrioventricular conduction was prominent resulted in hemodynamic changes that were limited to a mild decrease in LV *dP/dt* and elevation of right and left heart filling pressures. No untoward effects on coronary sinus hemodynamics or on global myocardial metabolism, insofar as reflected in $M\dot{V}O_2$ or MLE, were observed in these dogs. Unlike the findings of the study in halothane-anesthetized swine by Kates et al. (19), the lower plasma levels of diltiazem in our study were not associated with decreases in systemic blood pressure.

Loading doses or infusion rates of diltiazem similar to those used in this study have been associated with increases in coronary blood flow to nonischemic myocardium in dogs anesthetized with barbiturates or chloralose (6–9). We did not observe any change in CVR or $\dot{Q}_{CS}$, perhaps because vasodilation in our animals was already maximal in the presence of isoflurane. Skarvan et al. (26) found that the addition of diltiazem by infusion to achieve plasma levels of 129 ± 23 and 282 ± 32 ng·ml^{-1} to fentanyl-anesthetized dogs resulted in dose-dependent decreases in CVR and increases in $\dot{Q}_{CS}$. However, in their study, the subsequent addition of isoflurane (0.8 ± 0.1% and 1.3 ± 0.2%) during continuation of the higher infu-

Table 3. Plasma Epinephrine and Norepinephrine Levels in Arterial (A) and Coronary Sinus (CS) Blood

Group		n	Epinephrine (pg·ml^{-1})[a] Control	Epinephrine (pg·ml^{-1})[a] 30 min	Norepinephrine (pg·ml^{-1})[a] Control	Norepinephrine (pg·ml^{-1})[a] 30 min
I	A	7	373 ± 104	347 ± 88	163 ± 58	222 ± 50
	CS	6	99 ± 50	84 ± 35	66 ± 20	76 ± 25
II	A	8	249 ± 61	225 ± 44	128 ± 35	147 ± 39
	CS	7	82 ± 32	45 ± 12	150 ± 52	156 ± 49
III	A	8	292 ± 70	235 ± 38	210 ± 38	160 ± 44
	CS	7	85 ± 30	57 ± 13	133 ± 53	241 ± 42
IV	A	8	262 ± 63	350 ± 134	134 ± 48	223 ± 58
	CS	7	42 ± 13	79 ± 23	123 ± 36	204 ± 46

[a] Mean ± SEM; no difference between control and 30-min values in any group.

Table 4. Coronary Hemodynamics and Myocardial Metabolic Measures

	Group	n	Control[b]	30 min[b]
$\dot{Q}_{CS}$[a] (ml·min^{-1})	I	5	105 ± 15	100 ± 12
	II	7	164 ± 21	168 ± 29
	III	7	126 ± 19	133 ± 9
	IV	7	178 ± 30	159 ± 30
CVR[a] (mm Hg·ml^{-1}·min^{-1})	I	5	0.65 ± 0.10	0.65 ± 0.12
	II	6	0.47 ± 0.07	0.51 ± 0.11
	III	7	0.56 ± 0.10	0.48 ± 0.05
	IV	6	0.46 ± 0.11	0.48 ± 0.13
MLE[a] (%)	I	6	0.39 ± 0.05	0.31 ± 0.04
	II	7	0.41 ± 0.07	0.32 ± 0.04
	III	7	0.33 ± 0.05	0.25 ± 0.03
	IV	7	0.28 ± 0.04	0.25 ± 0.03
$M\dot{V}O_2$[a] (ml·min^{-1})	I	6	6.1 ± 1.3	6.5 ± 0.5
	II	5	13.5 ± 2.1	12.0 ± 2.2
	III	5	7.8 ± 1.0	8.9 ± 0.3
	IV	7	12.5 ± 2.4	12.0 ± 2.2

[a] Abbreviations: $\dot{Q}_{CS}$, coronary sinus blood flow; CVR, coronary vascular resistance; MLE, myocardial lactate extraction; $M\dot{V}O_2$, myocardial oxygen consumption.

[b] Mean ± SEM; no difference between control and 30-min values in any group.

sion rate of diltiazem did not result in any additional decrease in CVR. The addition of isoflurane under the circumstances of their study was found to decrease $\dot{Q}_{CS}$, which was associated with a decrease in aortic pressure. In addition, diltiazem levels were found to be increased, for the same infusion rate at their higher isoflurane concentration. Pharmacokinetic studies indicate that plasma diltiazem clearance is dependent upon hepatic blood flow (27). Though our study did not include unanesthetized controls, our intent was not to investigate the effects of isoflurane on the pharmacokinetics of diltiazem, but rather to achieve plasma levels less than 500 ng·ml^{-1} during isoflurane anesthesia by use of appropriate infusion rates.

Our finding that interference with intracardiac conduction was prominent at plasma levels that did not have measurable hemodynamic effects is consistent with other studies (18,28). The positive correlation of PR interval prolongation with plasma diltiazem level is useful when therapy is designed to achieve conduction effects without adverse hemodynamic side effects. Browne et al. noted a correlation of both PR interval and systemic blood pressure with plasma diltiazem level in conscious dogs administered diltiazem orally (17). Perhaps the absence of a vasodilating anesthetic contributed to their findings of decreased blood pressure at lower plasma levels of diltiazem.

The decrease in LV *dP/dt* in groups II–IV and the increase in filling pressures in groups III and IV after 30 min of infusion, without a significant decrease in SVR, are consistent with the findings of Kates et al., who found that the higher levels of diltiazem that did decrease blood pressure during halothane anesthesia were also associated with decreased LV *dP/dt* and cardiac output, and increased PAO pressures without a change in SVR (19).

Limitations of thermodilution $\dot{Q}_{CS}$ measurements, other than catheter-related complications, are maintenance of proper catheter position and ensuring adequate mixing of CS blood and the indicator. In addition to the steps detailed in the methods section to monitor the proper position of the catheter, in the present study at least 1 min was allowed to elapse after beginning the indicator infusion to permit thorough mixing with the CS blood before measurements were taken. Measurements of CS hemodynamics and of plasma lactate levels in CS blood reflect global functioning of the left ventricle and cannot distinguish regional differences. This study, however, was designed to evaluate diltiazem–isoflurane interactions on the normal cardiovascular system, where regional differences in myocardial function would not be expected. The lack of effect of diltiazem upon $\dot{Q}_{CS}$, CVR, $M\dot{V}O_2$, and MLE, as well as on plasma catecholamine levels is consistent with the overall benign hemodynamic effects observed in this study of these plasma levels of diltiazem in the presence of 1.5% isoflurane. Higher levels of diltiazem, at which further ventricular impairment and reduced systemic and coronary perfusion pressures are seen, may have different effects on myocardial oxygen balance and on autonomic responses. Varying the concentration of isoflurane or choosing a different anesthetic may well result in different cardiovascular effects for the same plasma diltiazem levels.

In summary, the most significant effect of plasma levels of diltiazem < 600 ng·ml^{-1} during isoflurane anesthesia in our dogs was impaired intracardiac conduction. The decreased LV *dP/dt* at the upper plasma levels in this study was not accompanied by decreased MAP or CI at these anesthetic levels. While no impairment of global myocardial oxygen balance was seen, neither did any increase in myocardial oxygen supply or reduction in two of the determinants of myocardial oxygen demand, i.e., afterload (MAP was unchanged) or preload (PAO was increased) occur. To the extent that animal data can be extrapolated to humans, the combination of reduced contractility, as reflected in LV *dP/dt*, and conduction impairment may necessitate caution if higher doses of diltiazem are inadvertently administered during clinical anesthesia with isoflurane. On the other hand, our data suggest that lower doses of diltiazem may be expected to have antiarrhythmic properties under clinical conditions by virtue of their ability to prolong atrioventricular conduction at low plasma levels in the presence of moderate concentrations of isoflurane without associated hemodynamic side effects.

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Technical Communication

Solubility of N_2O in Volatile Anesthetics Contributes to Vaporizer Aberrancy when Changing Carrier Gases

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It is well established that vaporizer output varies with changes in the composition of the gases flowing through the vaporizer. However, the question of whether the influence of the carrier gases on vaporizer output is a matter of differences in the gas densities, viscosities, or both or whether the influence reflects differences in the solubilities of the carrier gases in the volatile agent is unclear. Nawaf and Stoelting observed that enflurane output from Ohio vaporizers was greater in the presence of N_2O than with O_2 alone and suggested that differences in densities of the two gases could explain the variation in output (1). The effect of such differences might be that a variable amount of gas is shunted through the vaporizing chamber as the composition of the carrier gas changes. The alterations in output they observed were small and persisted for as long as N_2O was used as a carrier gas.

More recently, Gould et al. (2) examined vaporizer output during the transition from one carrier gas to another. They observed large variations in vaporizer output lasting up to 30 min when introducing or discontinuing N_2O. Gould et al. attributed these changes to the considerable solubility of N_2O in liquid volatile anesthetic (3). This would lead to N_2O either being absorbed by or liberated from the liquid anesthetic and thereby either would decrease or increase gas flow through the vaporizing chamber.

In flow over vaporizers, it is difficult to separate these physical phenomena because vaporizers are not compensated for density, viscosity, or the solubility of carrier gases in liquid anesthetic. We wished to clarify the degree to which the differential solubilities of carrier gases in liquid volatile anesthetic can influence vaporizer output, and the time course over which it occurs. Therefore, we measured vaporizer output with different carrier gases in a system in which density, viscosity differences between carrier gases, or both would not be expected to influence output.

Materials and Methods

Experiment 1

An Ohio Ethrane vaporizer filled with enflurane was used. Seventy percent N_2O in O_2 at 3 L/min was passed through the vaporizer with the dial set at 1%. The output was measured with a calibrated Chemetron mass spectrometer at 60-sec intervals. When output stabilized, N_2O was discontinued, and 30% O_2 in N_2 at 3 L/min was substituted. After output stabilized again, 70% N_2O in O_2 was reinstituted. All experiments were performed at 21°C.

Experiment 2

A Dupaco anesthesia machine with a Vaporator vaporizer was used. The operation of the Vaporator vaporizer is similar to that of a copper kettle. Oxygen is bubbled through the vaporizer from a flow meter, and the output is combined with a separate bypass gas for delivery to the anesthesia circuit. Vaporizer output is controlled by the operator who must know the vapor pressure of the anesthetic being vaporized (at a given temperature) to determine accurately the delivered concentration of volatile agent. Normally only O_2 passes through the flow meter supplying the vaporizer. However, the anesthesia machine was

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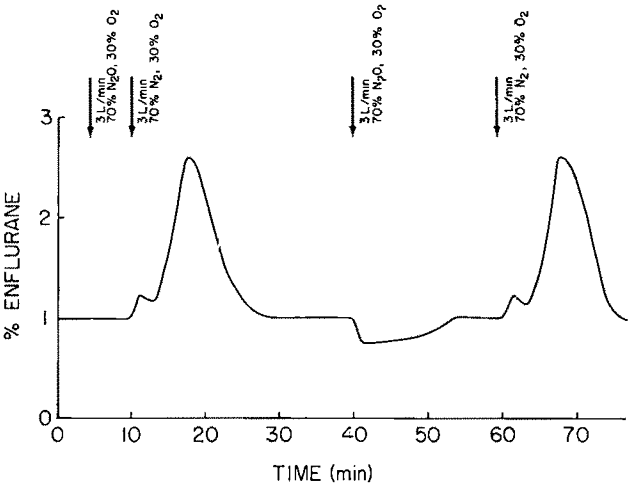

Figure 1. Ohio enflurane vaporizer output with different carrier gases.

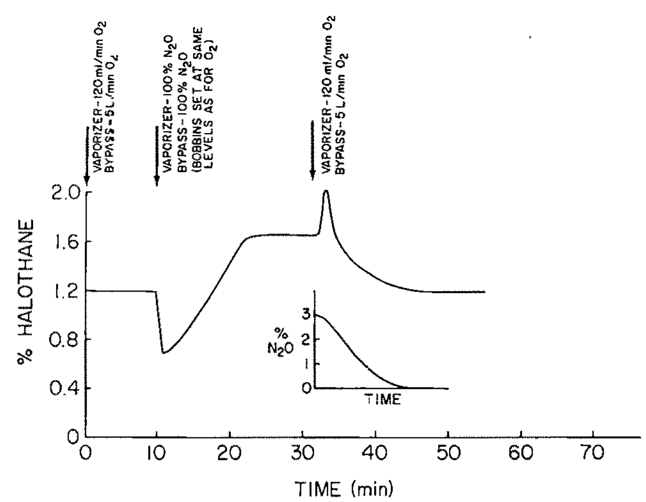

Figure 2. Halothane and N_2O output from Dupaco Vaporator when changing carrier and bypass gas from O_2 to N_2O to O_2.

modified so that it was possible to deliver either N_2O or O_2 (one gas at a time) to both the vaporizer's flow meter and the main O_2 flow meter. One hundred seventy ml of liquid halothane was placed in the Vaporator reservoir, and O_2 at 120 ml/min, as measured by the vaporizer's flow meter, was passed through the vaporizer. The vaporizer effluent was combined with a 5-L O_2 bypass flow from the main O_2 flow meter. Volatile agent and N_2O concentrations were measured with the mass spectrometer downstream from the point at which the vaporizer and bypass flows are combined. This was accomplished by sampling gas from the fresh gas delivery hose that ordinarily would be attached to the circle or other anesthetic delivery system. Once output stabilized, O_2 flow was discontinued, and N_2O was then passed through both the vaporizer's flow meter and the main O_2 (bypass) flow meter. The flow meters were adjusted to read exactly as before, that is 120 ml/min and 5 L/min for the vaporizer and main bypass flows, respectively (see discussion). When output stabilized, O_2 was substituted for N_2O and this sequence repeated. Concentrations of N_2O and halothane were recorded every 60 sec.

Results

Experiment 1

Figure 1 is a plot of the Ohio enflurane vaporizer output over time with the different carrier gases. Note the abrupt increase in enflurane output after changing gases from N_2O/O_2 to O_2/N_2 and the gradual return to baseline over the next 20 min.

Experiment 2

The concentrations of N_2O and halothane from the Vaporator are plotted in Figure 2. With O_2 as the carrier gas, output stabilized at 1.2%. After the change to N_2O, output decreased precipitously to 0.70% and then gradually increased over the next 10 min to stabilize at 1.64%. Switching gases from N_2O to O_2 at this point resulted in a sharp halothane output increase to 1.9% and then a gradual return to the 1.2% baseline over the next 12 min. The concentration of N_2O decreased rapidly (within 1 min) from 99%, stabilized at 3%, and then decreased gradually to zero over a time course that matched that of the decrease in halothane concentration.

Discussion

The results of experiment 1 are consistent with those of Lin (see his Fig. 7) (4). That is, after the transition from N_2O to O_2, vaporizer output increased abruptly, nearly tripling, and remained elevated for nearly 30 min. Conversely, substituting 70% N_2O for N_2 caused vaporizer output to decrease transiently by about 25% before returning to baseline. Lin attributed these changes to differences in viscosity between N_2O and O_2, which he speculated might alter the internal distribution of the bypass and vaporizing chamber flow as one gas replaces the other. However, Gould et al. (2), after examining results qualitatively similar to those of Lin, ascribed the observed aberrancy to the differences in solubility of N_2O and O_2 in liquid volatile anesthetics. Their conclusions were supported by the observation that the decreases in output that occurred while changing carrier gases from O_2 to N_2O could be prevented by presaturating liquid volatile anesthetics with N_2O (2). Furthermore, as noted earlier, studies from the same laboratory previously had determined that N_2O is highly soluble (4.19 and 4.77 ml $N_2O \cdot ml^{-1}$ of liquid halothane or enflurane, respectively) in volatile anesthetic liquids (3). In the studies reported by these two groups (2,4), it is not possible to separate the effects of the viscosity/density and solubility characteristics of the carrier gases because both influences may have been at work simultaneously. Our experiment 2 is an attempt to exclude these interactions.

However, there remain certain limitations in the design of our experiment 2. It is not possible to know the precise flow of N_2O passing through flow meters calibrated for O_2 other than by measuring flow directly. This was not done in the present experiment. When flow meters are used for gases other than those for which they are calibrated, differences in both viscosity and density can result in the occurrence of different flows at a given bobbin position (5). This probably explains why the baseline concentrations of halothane in experiment 2 were different for the two carrier gases (1.2% for O_2 vs 1.64% for N_2O) despite our maintaining constant bobbin positions.

Nonetheless, once the carrier gas had been changed from N_2O to O_2 or vice versa, vaporizer flow was fixed, and any flow meter inaccuracy or difference in density or viscosity between the gases could not have played a part in the changing output we observed to continue for between 10 and 20 min.

The results of our experiment 2 support the contention that N_2O dissolved in liquid enflurane or halothane accounted for the aberrance of the vaporizer's output. The decline in N_2O concentration in the gas exiting the vaporizer after changing gases from N_2O to O_2 precisely paralleled the decreasing output of halothane. By integrating the area under the N_2O output curve and multiplying by the total O_2 flow (5120 ml/min), one can derive the total amount of N_2O dissolved in the 170 ml of liquid anesthetic (806 ml). This number agrees reasonably well with that determined by Lampert et al. (i.e., 4.19 and 4.77 ml $N_2O \cdot ml^{-1}$ liquid halothane or enflurane, respectively) (3).

When a nonrebreathing system is used, the aberrant output resulting from changing carrier gases may be transmitted quickly and directly to the patient. This could result in inappropriate deepening or lightening of anesthesia. With circle systems, these changes might be of lesser consequence as a result of the circle's tendency to buffer changes in volatile agent concentration. Indeed, it was the rapidly fatal anesthetic overdoses we observed in our animal laboratory while changing carrier gases from N_2O/O_2 to N_2/O_2 when using the Ohio vaporizer, a nonrebreathing system, and controlled ventilation that prompted the present investigation.

In summary, the results presented here support the theory that the vaporizer output aberrancy that occurs after changing gases is influenced significantly by the relative solubilities of carrier gases in the liquid anesthetic. Furthermore, these results emphasize that clinically significant changes in vaporizer output may be induced by changing carrier gases. Regardless of the etiology, these relationships must be appreciated by practicing anesthetists.

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Clinical Reports

Hyperdynamic Cardiovascular Responses to Anesthetic Induction with High-Dose Fentanyl

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Anesthetic induction with high-dose fentanyl is a popular technique for use in patients with cardiovascular disease, because hemodynamic stability generally results (1–3). However, hypotension in association with decreased serum catecholamine levels may be observed when benzodiazepines are used in conjunction with fentanyl during induction (1,4). Conversely, the combination of fentanyl with pancuronium can cause tachycardia and myocardial ischemia during induction in some patients with coronary artery disease (5). These hyperdynamic responses may be mediated by antimuscarinic or sympathomimetic effects of pancuronium (6,7). We have also observed several instances in which anesthetic induction with fentanyl and a muscle relaxant other than pancuronium has been associated with clinically significant increases in heart rate and blood pressure. We report four such cases in which hyperdynamic responses were observed in unstimulated well-ventilated patients after administration of either a bolus or infusion of fentanyl, 50–100 μg/kg, in combination with either metocurine or a metocurine–pancuronium mixture (8). The hemodynamic responses observed suggest that the sympathetic nervous system may be involved in mediating occasional hyperdynamic responses to anesthetic induction with fentanyl. Finally, we present a fifth case that we think illustrates a drug interaction between fentanyl, pancuronium, and theophylline in an asthmatic patient with coronary artery disease.

Methods

All reported cases were encountered in the course of institutionally approved clinical trials for which the patients had given informed consent (5,9). Four patients underwent elective coronary artery surgery, and one underwent elective abdominal aortic aneurysm resection. All regular antianginal and antihypertensive medications were administered on the day of surgery. After premedication with 0.1 mg/kg morphine intramuscularly and 0.006 mg/kg scopolamine intramuscularly 60 min preoperatively, patients were transferred to the operating room where intravenous, radial arterial, and thermodilution pulmonary arterial catheters were inserted under local anesthesia. Electrocardiographic (ECG) lead V_5, systemic arterial pressure, pulmonary arterial pressure, and central venous pressure (CVP) were recorded continuously by a polygraph. Prior to induction all patients breathed 100% oxygen from an anesthetic machine. End-tidal carbon dioxide tension (ET_{CO_2}) was monitored continuously throughout induction. Patients having coronary artery surgery received $0.2 \times ED_{95}$ of a nondepolarizing relaxant prior to induction. Fentanyl, 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, was administered during induction to a total of 50 $\mu g \cdot kg^{-1}$. After loss of consciousness $1.3 \times ED_{95}$ of the nondepolarizing relaxant was administered over 2 min, and ventilation was manually controlled to maintain normal ET_{CO_2}. Anesthesia was induced in the patient undergoing abdominal aortic aneurysm surgery, with 100 $\mu g \cdot kg^{-1}$ fentanyl intravenously plus $1.5 \times ED_{95}$ of relaxant given as a rapid bolus. Ventilation was controlled to maintain normal ET_{CO_2} for 4 min after induction. In all patients normocapnia during manual ventilation was verified by arterial carbon dioxide measurements at the midpoint and end of the induction sequence. Complete hemodynamic measurements including thermodilution

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Table 1. Features of 5 Patients who Developed Hyperdynamic Cardiovascular Responses to Induction with Fentanyl

Patient number	Age (yr)	Sex	Associated conditions	Concurrent Drugs (mg/day)	Ejection fraction	Procedure	Relaxant ($1.5 \times ED_{95}$)	Intervention before intubation
1	75	M	—	none	—	Abdominal aneurysm	Metocurine–pancuronium	Nitroprusside
2	58	M	Hypertension	Propranolol 240 mg Isosorbide 80 mg Hydralazine 240 mg	0.77	Coronary bypass	Metocurine	Nitroglycerin
3	46	M	—	Propranolol 160 mg Isosorbide 120 mg	0.67	Coronary bypass	Metocurine–pancuronium	—
4	51	M	Diabetes mellitus	Propranolol 80 mg Nifedipine 40 mg	0.80	Coronary bypass	Metocurine–pancuronium	Nitroglycerin
5	62	M	Asthma	Verapamil 480 mg Isosorbide 120 mg Theophylline 600 mg	0.66	Coronary bypass	Pancuronium	Nitroglycerin Verapamil Propranolol

Table 2. Hemodynamics and Arterial Carbon Dioxide Tension before and after Anesthetic Induction with Fentanyl

Patient number	HR[a] (beats·min^{-1})		MAP[b] (mm Hg)		PCWP[c] (mm Hg)		CVP[d] (mm Hg)		CI[e] (L·min^{-1}·M^{-2})		Pa_{CO_2}[f] (mm Hg)		
	Before[g]	After[h]	Before	After	Before	After	Before	After	Before	After	Before	Mid	After
1	60	84	110	138	13	17	6	11	2.64	3.12	36	—	34
2	48	70	114	136	12	16	5	6	2.60	3.52	41	43	40
3	50	56	93	113	19	21	7	8	2.48	2.60	39	43	39
4	52	62	90	130	6	14	2	5	2.50	2.80	40	39	35
5	84	132	95	121	12	17	4	12	3.99	8.52	35	39	38

[a]Heart rate; [b]Mean arterial pressure; [c]Pulmonary capillary wedge pressure; [d]central venous pressure; [e]cardiac index; [f]arterial carbon dioxide tension; [g]Before, before induction; [h]After, after induction.

cardiac output measurements in triplicate were made prior to induction and at the end of the induction sequence. The patients were subsequently intubated.

Results

The demographic characteristics of the five patients are presented in Table 1. The hemodynamic consequences of induction are presented in Table 2. Polygraph recordings during induction in patients 1, 2, and 5 are illustrated in Figures 1–3, respectively. Heart rate, mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), CVP, and cardiac index (CI) increased in each patient, whereas arterial P_{CO_2} remained within the normal range (35–45 mm Hg). All patients were well oxygenated throughout. The most dramatic changes were noted in patient 5, an asthmatic who underwent coronary artery bypass grafting and in whom concurrent therapy included verapamil and theophylline. This patient developed electrocardiographic ST-segment depression. In all patients hyperdynamic responses developed gradually over a period of several minutes, although onset seemed more abrupt in the patient who received a 100-μg·kg^{-1} bolus of fentanyl (Fig. 1). Figure 2 is typical of the response in patients 2–4 during fentanyl (5 μg·kg^{-1}·min^{-1}) infusion with either metocurine or the metocurine–pancuronium combination. An initial decrease in arterial pressure coincides with loss of consciousness, but thereafter a steady increase develops that overshoots baseline values by the end of the induction sequence. Four of five patients required intravenous administration of vasoactive medications prior to intubation to control the hyperdynamic cardiovascular response (Table 1).

Discussion

The hyperdynamic responses observed in patients 1–4 occurred in response to intravenous administration of a large (50–100 μg·kg^{-1}) fentanyl dose in conjunction with either metocurine (0.42 mg·kg^{-1}) or a metocurine (0.10 mg·kg^{-1}) plus pancuronium (0.025 mg·kg^{-1}) combination. Metocurine can cause histamine-mediated tachycardia and hypotension but not hypertension (10). Larger doses ($2.0 \times ED_{95}$) of the metocurine–pancuronium combination have been administered to normal adults with no significant cardiovascular response (11). Because normal Pa_{CO_2} was maintained in all patients, the observed responses must be attributed either to fentanyl or to awareness in inadequately anesthetized paralyzed patients.

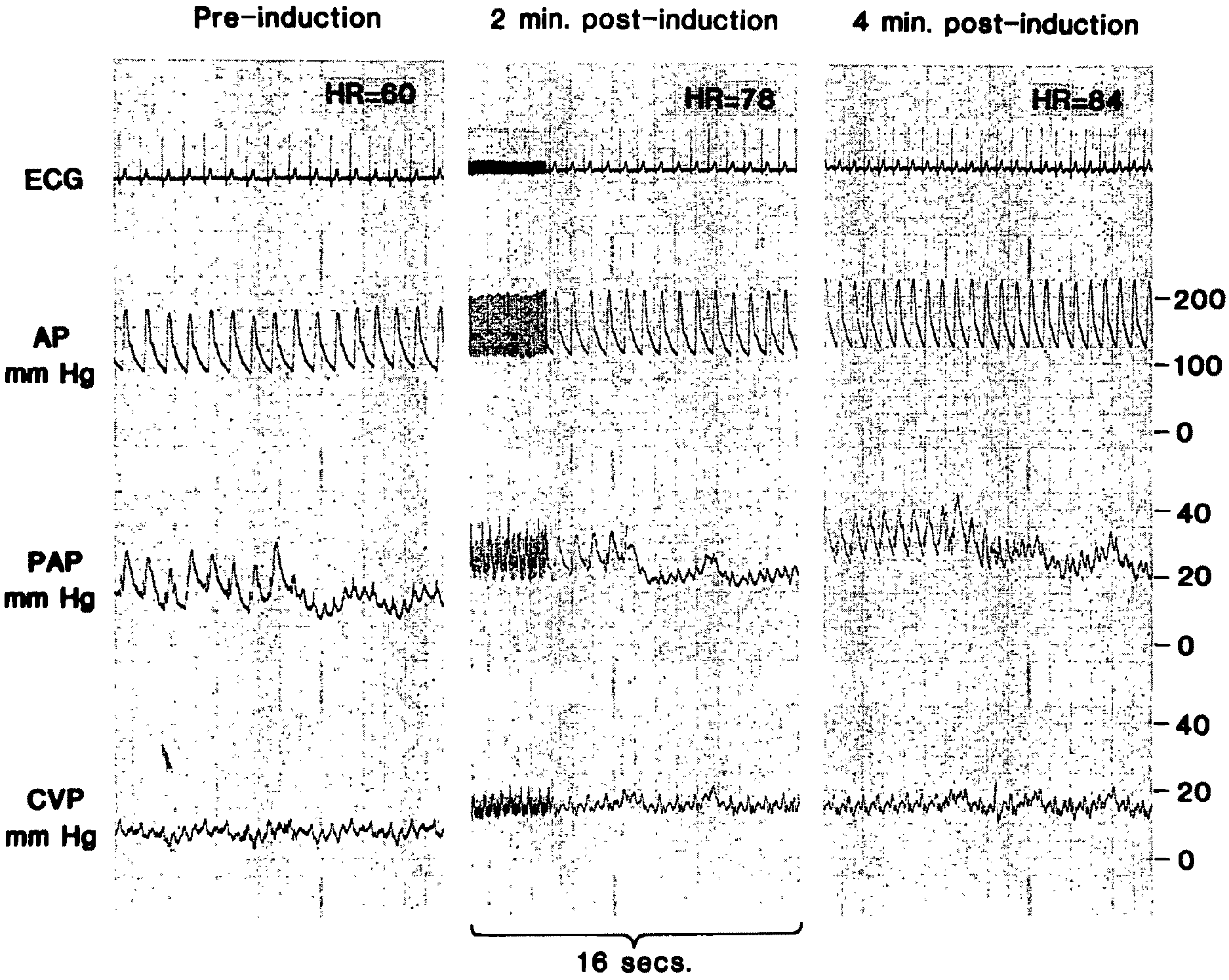

Figure 1. Polygraph recording during induction in patient 1, who underwent abdominal aortic surgery after a bolus of 100 μg/kg fentanyl and metocurine–pancuronium 1.5 × ED_{95}.

The combination of tachycardia, hypertension, increased filling pressures, and increased cardiac output observed strongly suggests a role for the sympathetic nervous system in mediating these effects. Fentanyl causes increased norepinephrine release from sympathetic nerve endings in isolated canine coronary arteries (12). Fentanyl also appears to inhibit neuronal reuptake of norepinephrine in both dogs and rabbits (12,13). Fentanyl administration is associated with increased urinary catecholamine excretion in dogs, but diazepam reverses this effect (14). The serum catecholamine response to high-dose fentanyl administration in patients with heart disease is somewhat controversial. Some authors report decreased or unchanged serum catecholamines (15,16), whereas others have noted increases (4,17). The explanation of these disparate results is unclear, but factors such as premedication and fentanyl dose may be involved. None of these data are incompatible with the hypothesis that the sympathetic nervous system might mediate idiosyncratic responses such as those we describe in this report.

If the sympathetic nervous system is involved in mediating the hyperdynamic circulatory responses to fentanyl we have observed, then more dramatic responses might be expected when other sympathomimetic agents are used in combination with high-dose fentanyl. We believe that the extreme tachycardia, hypertension, and increased cardiac output, and the ECG change observed in patient 5 (Fig. 3) may represent such an interaction. β-Adrenergic blocking agents were contraindicated in this theophylline-treated

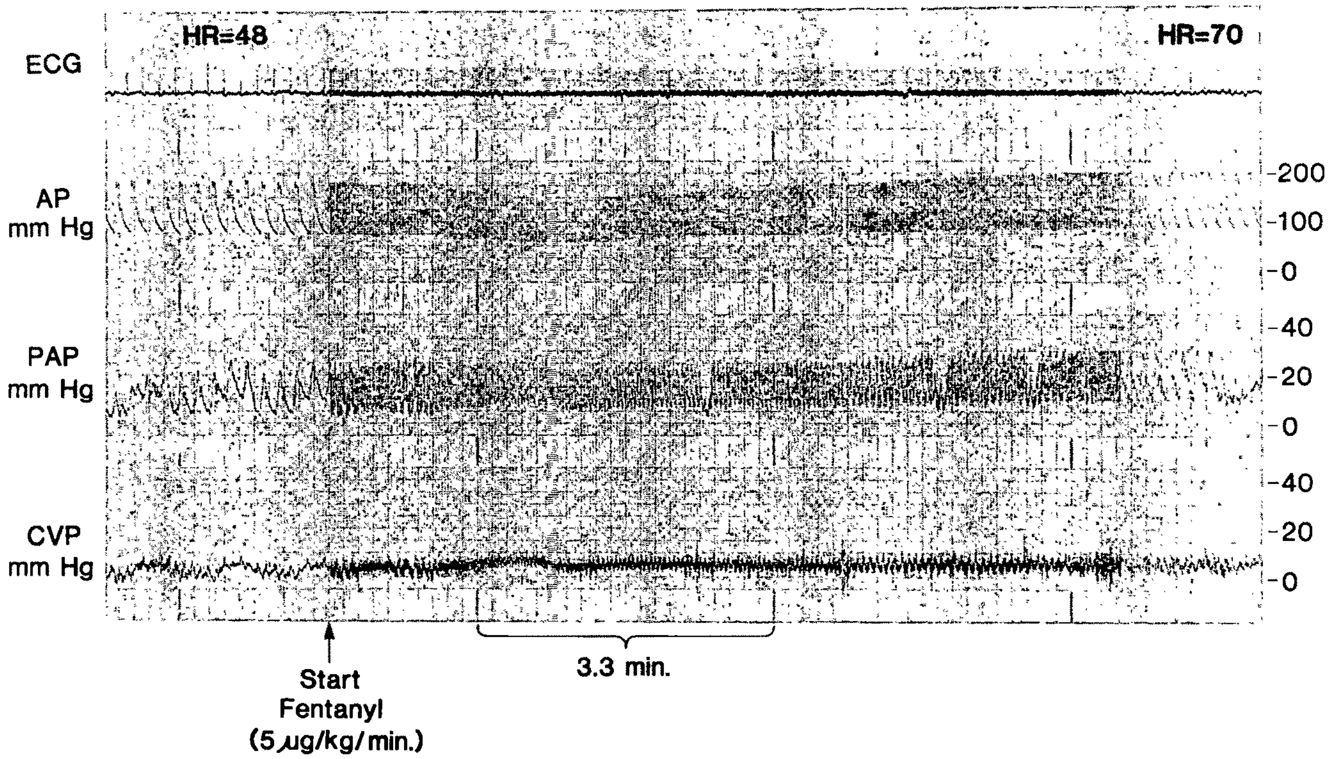

Figure 2. Polygraph recording during induction in patient 3 who underwent coronary artery surgery after induction with 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ fentanyl for 10 min plus metocurine 1.5 × ED_{95}.

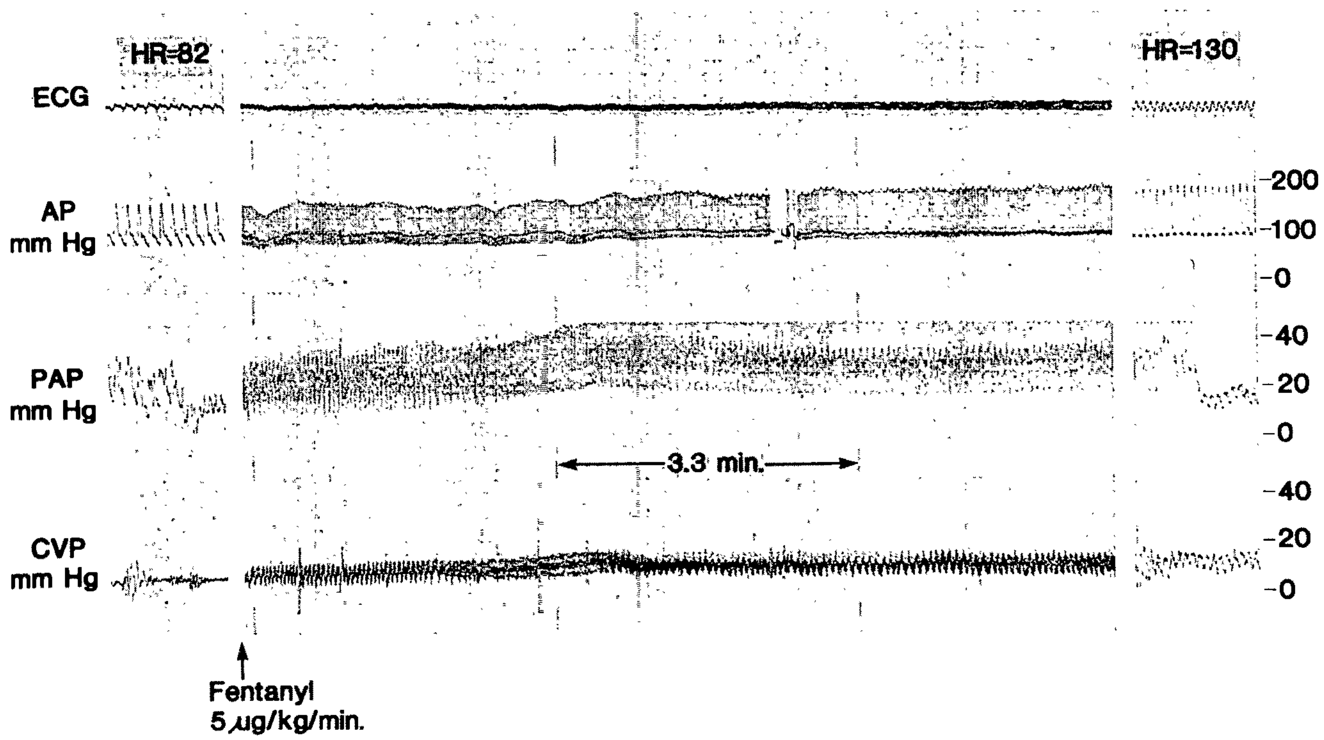

Figure 3. Polygraph recording during induction in patient 5 who underwent coronary artery surgery after induction with 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ fentanyl for 10 min and fentanyl–pancuronium 1.5 × ED_{95}. A severe hyperdynamic reaction resulted in this non-β-blocked asthmatic, possibly representing a drug interaction among fentanyl, pancuronium, and theophylline.

asthmatic. The combined effects of fentanyl plus the antimuscarinic and sympathomimetic effects of pancuronium in a patient with phosphodiesterase inhibition may have caused the serious reaction observed.

Cases 1–4 reported here were gleaned from a total of 40 patients who received similar anesthetics during various clinical investigations, thus indicating an incidence of approximately 10%. We have observed numerous similar cases in our clinical practice occurring with about this frequency. We can only speculate as to why such cases have not previously been reported. Variations in anesthetic technique enumerated above may influence the incidence of such responses. Pancuronium has been used widely in combination with fentanyl and undoubtedly many adverse events have been attributed solely to that relaxant. Other reactions have probably been mistakenly attributed to increased Pa_{CO_2} during induction even when this variable was not monitored. Often muscle rigidity associated with fentanyl induction necessitates early muscle relaxant administration to apparently conscious patients. Presumably this might lead to a sympathetic response, although the patients are subsequently amnesic for these events. This explanation seems inadequate to explain the responses observed in our patients but cannot be ruled out.

In summary, hyperdynamic cardiovascular responses may occur in occasional patients in whom anesthesia is induced with high-dose fentanyl. Such reactions are potentially harmful in patients with cardiovascular disease. The incidence of such responses may vary depending upon premedication, fentanyl dose, rate of fentanyl administration and use of adjunctive agents, especially β-adrenergic blocking agents and benzodiazepines. Drug interactions may result when fentanyl is used with sympathomimetic agents.

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Reversible Loss of Somatosensory Evoked Potentials during Anterior Cervical Spinal Fusion

Tod B. Sloan, MD, PhD, Ann K. Ronai, MD, BS, PhD, and Antoun Koht, MD

Occlusion of the carotid artery has been reported as a complication of retractor placement for anterior cervical spine surgery (1). Failure to detect this occlusion can possibly cause cerebral ischemia and consequent cortical damage. Palpation of the temporal artery pulse has been used as a means of detecting vascular occlusion, but anatomical variations and inability to locate the pulse intraoperatively can make this technique unreliable for monitoring during surgery.

Somatosensory evoked potentials (SSEP) have been used during surgery on the spinal column as a means of continuously assessing cord function. For surgical procedures in the cervical region, SSEP from median or posterior tibial nerve stimulation may be used for the monitoring of operations in the high or low cervical spine, respectively.

Somatosensory evoked potentials have also been used for the detection of central or brainstem ischemia (2,3). In addition, median nerve evoked responses have been used as a method of monitoring adequate cerebral perfusion during carotid endarterectomy (6).

We present three case reports of patients undergoing operations for anterior cervical spinal fusion, in which changes in the SSEP signal occurred concurrently with retractor placement and returned to baseline after the retractor was repositioned.

Case Reports

Eighteen patients undergoing anterior cervical laminectomy with bone graft placement and fusion during the 23-month period ending February 1985 were monitored intraoperatively with SSEP. Stimulation of the median (MN) (for operations cephalad to the sixth cervical vertebrae) or posterior tibial nerves (PTN) was conducted with a 300-μsec square-wave pulse at a rate of 8.5/sec and of constant current at least 2 mamp above the determined motor threshold. The cortical evoked potentials were recorded using sterile subdermal needle electrodes placed over the contralateral hand area (2 cm posterior to C3 or C4 of the international 10–20 system) or foot area (midline 2 cm posterior to Cz) for MN and PTN, respectively, and cervical spine response measured posteriorly over the second vertebral body. A reference subdermal electrode was placed at the midline on the forehead (Fz) and a silver/silver chloride ground electrode on the shoulder. The resulting electrical responses from 250 to 500 stimulations for 50 msec (MN) or 100 msec (PTN) after the stimulus were amplified, filtered, and digitized with a Nicolet CA 1000 signal averager. Bandpass filtration was set for passage between 5 and 250 Hz. Sixty cycle notch filtration was not utilized.

During the operation evoked potentials were recorded continuously from unilateral stimulation (alternating right and left). Abrupt changes in latency or amplitude of the cervical cord or cortical responses were evaluated for associated surgical, technical, physiologic, and anesthetic changes.

With the exception of Case 3, these patients were positioned supine with the neck hyperextended. The surgical procedure in these cases involved exposure of the cervical spine using an anterior approach. The skin was incised using a low collar incision and the platysma split along the anterior border of the sternocleidomastoid muscle. The trachea and esophagus were retracted medially and the carotid artery and sternocleidomastoid laterally with a Cloward retractor. When the spine was exposed, the intervertebral discs were removed and tibial or iliac crest bone graft placed to accomplish fusion.

In these 18 cases, SSEP deteriorations (reduction in amplitude to less than 50% of baseline and/or increase in latency from baseline of at least 10%), occurred in four cases. In one case the change was at-

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tributed to a technical problem (electrode disconnected). In three patients, the SSEP deterioration occurred after the placement of anterior neck retractors and it promptly returned to baseline after retractor adjustment.

Case 1

A 46-yr-old, 84-kg male was admitted to the spinal cord intensive care unit with anterior displacement and compression fracture of the seventh cervical vertebrae. A vertebral body fragment was seen in the x-ray protruding into the spinal canal by 25%. Neurologic examination revealed a unilateral C7 radiculopathy.

The operation performed was C6–T1 anterior fusion. The patient was monitored intraoperatively with posterior tibial SSEP. After premedication with diazepam (10 mg orally) and morphine sulfate (8 mg intramuscularly), he was brought to the operating room awake, where a blind nasal intubation of the trachea was accomplished using nasal cocainization and intravenous sedation with diazepam (2.5 mg) and fentanyl (100 μg). After intubation anesthesia was induced with 375 mg sodium thiopental. During the 3.5-hr procedure, anesthesia was maintained with fentanyl (total dose 1.75 mg), pancuronium (total dose 5 mg), and halothane (0.5–0.6% inspired) with controlled ventilation with oxygen (total flow 500–1000 cc/min). Shown in Figure 1 are several SSEP tracings taken during the operation from the postinduction baseline (top tracing) through the conclusion of surgery (bottom tracing). Cervical spine recordings were technically unsatisfactory for monitoring.

Deterioration of the SSEP with decreased amplitude and increased latency occurred approximately 4 min after soft tissue retraction in the neck was begun (Point **A**), but before spinal manipulation occurred. At this time the blood pressure was 145/85 and ventilation was unchanged. During a search for related events, the temporal artery pulsation was found to be absent unilaterally, and the carotid retractor was repositioned (Point **B**), with immediate return of the temporal artery pulse and recovery of the SSEP to near preclamp baseline by 12 min. Surgery subsequently proceeded uneventfully, and the patient was discharged 16 days later with no new detectable neurologic defects.

Case 2

A 35-yr-old, 86-kg male presented with multilevel cervical and lumbar radiculopathies thought to be secondary to a fall 6 yr previously. Prior to this operation

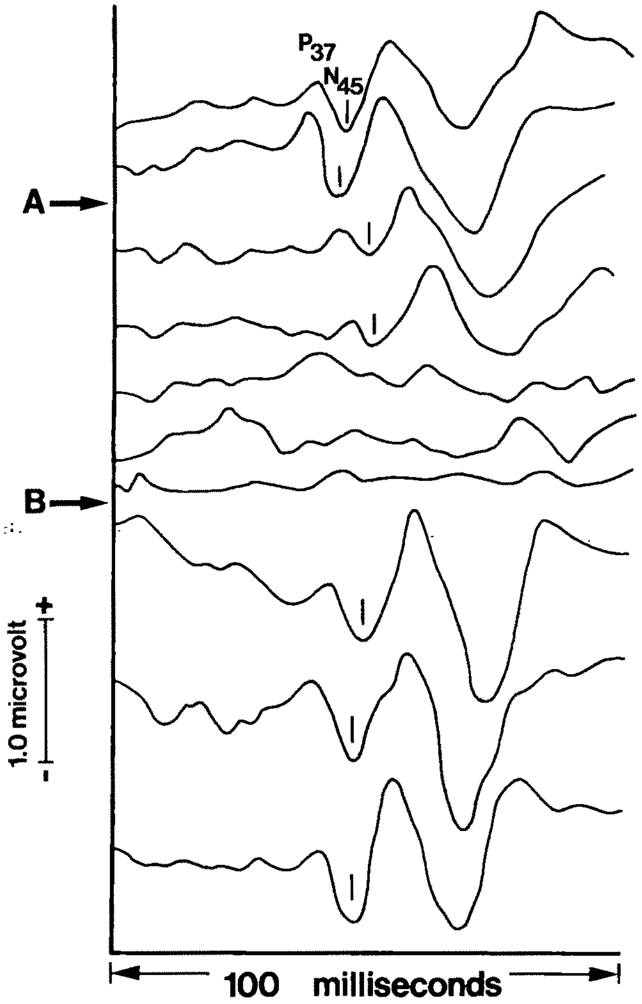

Figure 1. SSEP tracings for Case 1. Serial SSEP tracings taken from right median stimulation from beginning of surgery (*top*) through surgical closure (*bottom*). Complete loss of recognizable cortical evoked responses from posterior tibial nerve stimulation is seen after placement of anterior neck retractor (**A**). These responses return following replacement of the retractor (**B**). The monitoring peaks of interest are marked by P_{37} and N_{45}.

he had undergone posterior cervical laminectomy with fusion as well as lumbar laminectomy.

Anterior cervical fusion between C5–C6 and C6–C7 was planned. He was premedicated with morphine sulfate (8 mg intramuscularly). Intubation of the trachea was accomplished orally after the induction of general anesthesia with 500 mg of thiopental. Fentanyl (total 2.0 mg), pancuronium (total dose 10 mg), and isoflurane (0–0.3% inspired) were used for maintenance of anesthesia during controlled ventilation with oxygen (total fresh gas flow 1 L/min) for 2 hr. Transcervical anterior disk removal and removal of the cartilagenous endplate with interbody fusion was performed, along with the removal of an osteophyte at these levels.

The anterior neck retractor was positioned early in the surgical course, and a reduction in evoked potential amplitude was seen within 3 min. Recordings from the cervical spine were unchanged. The blood pressure at this time was 102/60 and ventilation unchanged. Palpation of the temporal artery was limited by the surgical draping, and a loss of pulsation was difficult to discern. However, removal and repositioning of the retractor was associated with immediate return of the temporal pulse and return of the SSEP to preretraction baseline within 6 min. The procedure was finished uneventfully, and the patient had partial resolution of his radicular pain.

Case 3

A 54-yr-old female presented after previous bilateral radical neck excisions (with unilateral carotid ligation), mandibular resection and wide soft tissue removal of a squamous cell carcinoma on the floor of the mouth, and radiation therapy. She had developed osteoporosis with flexion deformity of the cervical spine secondary to vertebral collapse of the second cervical vertebrae with unilateral muscular weakness. Surgical correction of her kyphotic deformity and spinal fusion were planned.

After premedication with atropine sulfate (0.4 mg intramuscularly), she was brought to the operating room where intubation of the trachea was accomplished via the nasal route using topical anesthesia (5% cocaine nasally, 4% lidocaine transtracheally), intravenous sedation (5 mg diazepam, 100 μg fentanyl), and flexible bronchoscopic guidance. After intubation, anesthesia was induced with thiopental (250 mg). Anesthesia for the 7-hr procedure was maintained using fentanyl (total dose 2.5 mg), pancuronium (total dose 10 mg), isoflurane (0–0.5% inspired), and controlled ventilation (total fresh gas flow 700 cc/min).

The procedure was conducted with a combined anterior and posterior approach to the cervical vertebrae in a semi-sitting position. Somatosensory evoked potentials were monitored by stimulation of the median nerve. Electrodes could not be placed in the posterior cervical spine. Access to the temporal artery pulsations by the anesthesiologist was not possible due to the patient's position and location of the surgical drapes. As with the previous cases, loss of evoked response occurred during the procedure within 5 min of retractor placement, at a time when the blood pressure (120/65) and ventilation were unchanged. The SSEP returned within 10 min after retractor removal. Her procedure was successfully completed, and her postoperative course was without perioperative neurologic deterioration.

Discussion

In patients at risk for spinal cord as well as cortical ischemia, SSEP monitoring may provide a valuable method to reduce morbidity. In these patients the reversible loss of both SSEP and, in two cases where it could be palpated, temporal artery pulsations suggests the SSEP change was related to carotid occlusion. Because the incidence of cerebral damage in this surgery is low (1), it is not known whether these patients would have sustained neural damage had these changes been left uncorrected. Experimental studies in occlusive vascular models suggest these changes could lead to adverse outcome (2–5), and the incidence of stroke with occlusion of one carotid for endarterectomy can vary from 0.3 to 3% (7).

In cases of carotid arterial occlusion, the occurrence of neurologic dysfunction from cerebral ischemia depends on vascular supply from the vertebral basilar arterial system, the contralateral carotid artery, and an intact circle of Willis. In patients with absent vessels (such as case 3, in whom the contralateral carotid artery was absent), reduced vertebral basilar flow (as can occur with hyperextension of the neck as in positioning for this surgery), or with functionally incomplete circle of Willis (seen in 27.4% of normal brains (8)), abrupt reduction in carotid flow may comprise cerebral blood flow. Anatomically, the middle cerebral artery (MCA) originates at the junction of the internal carotid artery and the circle of Willis, making it a likely candidate for reduced blood flow in these circumstances. Because the sensory cortex of the contralateral hand is supplied by the MCA, SSEP monitoring of the median nerve may detect such ischemia. Experience using median nerve SSEP monitoring during carotid endarterectomies (6) has confirmed this possibility.

Because SSEP changes in our three patients were not bilateral (i.e., both median nerves or both cerebral hemispheres), it is unlikely that they represented anesthetic or physiologic alterations (e.g., hypotension, ventilatory changes, or hypothermia). The unchanged cervical spinal response in case 2 suggests the abnormality was cephalad to the cervical spine and, therefore, consistent with cerebral ischemia.

The potential detection of cerebral ischemia or altered spinal cord function during surgical procedures has made SSEP monitoring an attractive adjunct to monitoring during operations where there is risk of central nervous system complications. An increase in latency and a reduction of SSEP amplitude were consistent with potentially deleterious conditions in the present three patients. The observed changes are consistent with those seen in reduced cerebral blood flow from carotid occlusion (6) or middle central artery occlusion (3–5). The reversibility of the deterioration with repositioning of the retractor in all three and the confirmation of loss of temporal artery pulsation in two strongly suggest that the changes were related to carotid artery occlusion.

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Hazardous Placement of a Robertshaw-Type Endobronchial Tube

Jerry A. Cohen, MD, Richard A. Denisco, MD, Thomas S. Richards, MD,
Edward D. Staples, MD, and Arthur J. Roberts, MD

Operations on the thoracic aorta may be facilitated by inserting an endobronchial tube to improve exposure of the thoracic aorta so that the left lung can be collapsed while the right lung is ventilated (1,2). Because right endobronchial intubation could compromise ventilation to the upper lobe of the right lung, we selected a Robertshaw-type left double-lumen endobronchial tube for a patient who required repair of a descending thoracic aortic aneurysm.

Case Report

A 76-yr-old man presented with a 3.5-month history of intermittent, dull chest pain localized to the left subclavicular region. He did not have substernal pain. His physician interpreted his chest radiograph as characteristic of an aneurysm of the descending thoracic aorta. The trachea was not deviated. After admission to the hospital, the patient's subclavicular chest pain increased when his systolic arterial blood pressure exceeded 120 mm Hg, but his chest radiograph was unchanged and his electrocardiogram demonstrated no acute changes. He was treated with propranolol, 10 mg, every 6 hr and scheduled for surgical repair of the aortic aneurysm. A computed tomographic scan showed an aneurysm, 12 cm at its largest diameter, involving the distal aortic arch and extending to the diaphragm.

Physical examination demonstrated an elderly man who was edentulous, with good range of motion in both neck and jaw. His lungs were clear to percussion and auscultation. Heart rate was regular, and there were no murmurs or extra sounds. Medical history was noncontributory except for the recent onset of paralysis of the left vocal cord. Routine laboratory findings were unremarkable. Preoperatively, arterial blood pressure was 90–150 mm Hg systolic and 60–110 mm Hg diastolic. Pulse ranged from 70 to 80 beats/min.

The patient was premedicated with morphine sulfate, 10 mg, propranolol hydrochloride, 10 mg, and scopolamine hydrobromide, 0.3 mg. In the operating room, a 20-gauge Teflon catheter was inserted in the right radial artery, and a 7.5-French triple-lumen, thermodilution catheter was inserted through the right internal jugular vein. One 16-gauge catheter was placed in the right arm and another in the left arm. Anesthesia was induced with fentanyl, 15 μg/kg, and maintained with 50% nitrous oxide in oxygen and 0.5–1% isoflurane. Pancuronium bromide, 0.15 mg/kg, was given to provide muscle relaxation.

The glottis was exposed and a 37-French left-sided, Robertshaw-type double-lumen endobronchial tube (Bronchocath) was inserted into the trachea, turned leftward, and advanced beyond the carina. Occlusion of each lumen demonstrated that the right rather than left main stem bronchus had been intubated. Repeated attempts to reposition the tube into the left main stem bronchus failed.

It was decided to attempt placement by directly visualizing the tracheobronchial tree with the aid of a fiberoptic bronchoscope. The endobronchial tube was withdrawn into the trachea and a 3.5-mm fiberoptic bronchoscope was inserted to the tip of the bronchial section of the endobronchial tube. The tube and bronchoscope were advanced together. Even when manipulated under direct visualization, the tube deviated from the left main stem bronchus and entered the right. The tube and bronchoscope were withdrawn into the trachea, and the bronchoscope was advanced beyond the tube into the orifice of the proximal left main stem bronchus. We then attempted to use the bronchoscope as a guide over which to pass the endobronchial tube. This failed twice when the tube would not enter the left main stem bronchus. The tube was withdrawn and a 35-French Robertshaw-type double-lumen endobronchial tube was substituted. The smaller tube was advanced with the bronchoscope again serving as a guide. The proximal

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left main stem bronchus was finally entered, and it was then seen to be narrowed approximately 40%. The narrowed bronchus resisted gentle attempts at further advancement of the bronchoscope. The tracheal and bronchial cuffs were then inflated until the air leaks around each cuff were minimal, but the endobronchial cuff isolated the left lung only when moderate inward pressure was applied to the endobronchial tube.

A left thoracotomy was performed, and exposure of the operative site was enhanced by deflating the left lung. An aneurysm, 6–7 cm in diameter, extending from the left subclavian artery to the diaphragm was found to be compressing the left main stem bronchus close to the bifurcation of the trachea. Both the tracheal and bronchial lumina were compressed. Furthermore, the aneurysm adhered tightly to the lung immediately adjacent to the left main stem bronchus.

Sodium nitroprusside was used to control the systolic blood pressure, and the thoracic aorta was clamped at the level of the subclavian artery and at the diaphragm. The aneurysm was incised, its contents evacuated, and a 30-mm, preclotted, woven Dacron graft was sutured within the aneurysm sac in an end-to-end fashion. The patient was discharged on the nineteenth postoperative day after a slow but uneventful recovery.

Discussion

The presence of vocal cord paralysis in this patient should have alerted us to the possibility that the aneurysm might have been compressing mediastinal structures. Vocal cord paralysis, usually on the left as in this case, is caused by compression of the recurrent laryngeal nerve (3–6) and may be an early sign of compression of the tracheobronchial tree (4,6). When the aneurysm is large enough to compress the tracheobronchial tree and lung, dyspnea, stridor, and cough are often present (3,4). These signs were absent in our patient. Not until the relationships of the bronchus and the aneurysm were directly visualized by surgical exposure did the full significance of the bronchial narrowing and the potential for a lethal error become obvious.

"Blind" placement of a double-lumen endobronchial tube is usually not difficult. Repeated failure of the bronchial extension tube to enter the appropriate bronchus, however, may signal an obstruction or deviation of the bronchus or trachea. Large aneurysms of the descending aorta can be an especially hazardous cause of bronchial obstruction. In such cases, forcing the endobronchial tube into position could rupture the aorta as well as the bronchus. Although this hazard could be avoided with the use of a right-sided double-lumen endobronchial tube, the difficulties of assuring adequate ventilation of the right upper lobe, even with a slotted cuff, make this alternative unattractive. The use of a bronchial blocker, such as a Fogarty occlusion catheter, to isolate the left lung is a rarely used (7) but reasonable alternative to bronchial intubation (8). It is not usable when, as in this case, the bronchial obstruction is proximal to the takeoff of the left upper lobe bronchial segment. Other potential hazards of endobronchial intubation include bronchial bleeding, perforation, or rupture caused by overinflating the cuff or malpositioning the tip (9,10). We recommend the use of fiberoptic bronchoscopy whenever difficulty is encountered in placing an endobronchial tube, especially in the presence of tracheal deviation or vocal cord paralysis, so that airway manipulation can be carried out under direct visualization. Advancing the endobronchial tube beyond a narrow segment of bronchus or against resistance is unacceptably hazardous.

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Letters to the Editor

Scavenging of Capnometers

To the Editor:

In a recent issue of your journal (1985;64:378) there was a letter to the editor titled "Capnographs: A New Operating Room Pollution Hazard?" The letter described the potential hazard of gases exhausted through CO_2 monitors and included a particular referral to the Puritan–Bennett model.

Although the risk is minimal, as pointed out by the authors, we share their concern for a healthy and safe OR environment. To address this issue, we made available beginning in April 1984 a Return Gas Kit (Part number 222014) capable of being used with our OR gas monitors (CO_2 and Anesthetic Agent). The kit includes a bacteria filter, return tube, and standard 22-mm luer adapter for connecting into a scavenging system.

We appreciate the authors' interest in this issue and always welcome constructive input regarding product needs and requirements.

Robert J. Conley
Puritan–Bennett Corporation
Wilmington, MA 01887

Verapamil Treatment of Intractable Reperfusion Ventricular Tachycardia/Fibrillation

To the Editor:

Kapur et al. have reported a patient undergoing coronary artery bypass surgery in whom verapamil was used to terminate ventricular arrhythmias that were refractory to traditional therapeutic measures (1). We experienced a similar response to verapamil in a patient undergoing aortic valve replacement in whom we could not terminate cardiopulmonary bypass because of recurrent ventricular tachycardia/fibrillation despite the use of lidocaine, bretylium, and multiple DC countershocks.

An 18-yr-old male who had severe rheumatic aortic regurgitation associated with a dilated, poorly contracting left ventricle was scheduled for aortic valve replacement. He was premedicated with morphine, 10 mg, scopolamine, 0.4 mg, and promethazine, 25 mg. Prior to induction of anesthesia, the patient was monitored by an ECG, an intraarterial pressure line, and a Swan–Ganz catheter. Baseline blood pressure was 140/70 mm Hg, the ECG showed normal sinus rhythm at a rate of 85 beats/min, and the pulmonary capillary wedge pressure (PCWP) was 15 mm Hg. Anesthesia was induced with intravenous diazepam, 0.2 mg/kg, fentanyl, 20 μg/kg, and alcuronium, 0.3 mg/kg. After induction of anesthesia and tracheal intubation, the blood pressure was 100/50 mm Hg, heart rate 75 beats/min, and PCWP 10 mm Hg. After midsternotomy, cardiopulmonary bypass was started, and moderate hypothermia (27°C) was induced. The aorta was then cross-clamped, and 2000 ml of cold potassium cardioplegia solution infused at the root of the aorta to induce cardiac asystole. The aortic valve was replaced, and the aortic cross clamp was removed. The clamping time was 48 min. At that time the perfusion pressure was 80 mm Hg; the esophageal temperature 35°C; and the arterial blood gases revealed Pa_{O_2} to be 375 mm Hg; Pa_{CO_2}, 38 mm Hg; pH, 7.42; and base deficit, 0. Serum sodium was 129 mEq/L and potassium 4.0 mEq/L. However, cardiopulmonary bypass could not be terminated because

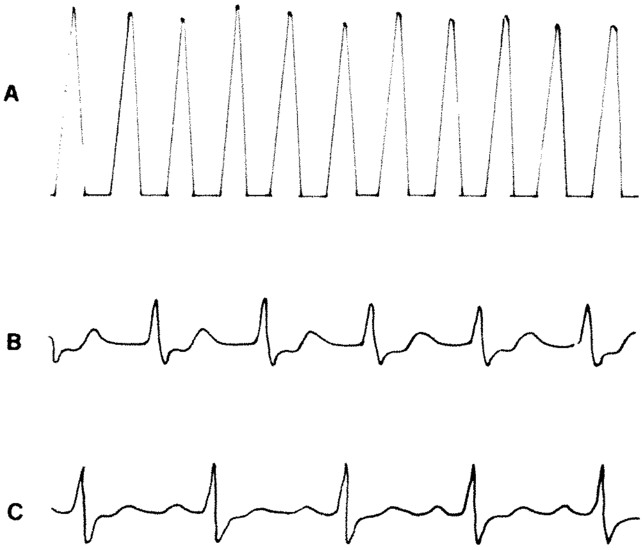

Figure 1. ECG tracings before and after the administration of 5 mg verapamil. (**A**) Ventricular tachycardia prior to injection of verapamil. (**B**,**C**) The effect of verapamil, which changed the ventricular tachycardia into nodal rhythm (**B**), and then normal sinus rhythm (**C**).

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of recurrent refractory ventricular fibrillation/tachycardia that followed unclamping of the aorta and that did not respond to repeated doses of lidocaine (2 mg/kg), bretylium (5 mg/kg), or multiple DC countershocks. During a paroxysm of ventricular tachycardia, one single bolus of verapamil, 0.075 mg/kg (5 mg), was injected intravenously. Without further DC countershocks, the ECG reverted rapidly to nodal, followed by normal, sinus rhythm (Fig. 1). The cardiopulmonary bypass could be terminated, and the blood pressure stabilized at 100/50 mm Hg, the heart rate at 100 beats/min, PCWP at 9 mm Hg, and the cardiac output at 5.3 L/min. Arrhythmias did not recur, and no further doses of verapamil were necessary.

The effectiveness of verapamil, a calcium channel blocker, for control of recurrent ventricular reperfusion arrhythmias suggests that calcium-dependent ionic currents may play an important role in the genesis and perpetuation of life-threatening ventricular arrhythmias of the acutely ischemic myocardium (2). Intractable reperfusion ventricular arrhythmias can occur whether the patient has a normal cardiac function (1) or obstructive hypertrophic cardiomyopathy (3). Our report shows that it can also occur in patients with pure regurgitation lesions associated with myocardial dilatation.

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Fentanyl and Fertilization

To the Editor:

I read with interest the article by Bruce et al. on the effect of fentanyl on fertilization and early development of sea urchin eggs (Anesth Analg 1985;64:498–500). The authors make reference in this article to the use of fentanyl in the anesthetic management of laparoscopic follicle aspiration for ovum retrieval in in vitro fertilization. They conclude that fentanyl did not inhibit fertilization or early development in sea urchin eggs, and therefore it might be considered for use in the anesthesia for follicle aspiration. However, the opioid anesthetics are known to produce or enhance the release of prolactin, which can create conditions in the endometrium that disfavor implantation of a zygote.

Embryo transfer commonly takes place within 48 hours of ovum retrieval, and although it seems empirically sound to assume that the anesthetics present in the ovum have dissipated, the effect of the anesthetic drugs on the patient's endometrium must also be considered.

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In Response:

Dr. Watson's point that prolactin levels increase during anesthesia is both well taken and well known. Whether this changes the endometrium so as to disfavor implantation two days later has not been established but is certainly possible. Centers doing human in vitro fertilization have had good results with fertilization but only fair results establishing pregnancy. Perhaps prolactin effects on the endometrium are responsible for this.

Our study addressed the effect of fentanyl on marine oocyte fertilization. Human oocyte fertilization is done 4–6 hr after follicle aspiration, not 48 hr, when Watson believes it "empirically sound to assume that the anesthetics present in the ovum have dissipated." We showed that fentanyl did not inhibit in vitro fertilization and early development of sea urchin eggs. We do not regard fentanyl as an "anesthetic," but suggest that it might be useful in anesthesia for follicle aspiration on the basis of our findings. If anyone believed we were claiming to have discovered the definitive technique for follicle aspiration anesthesia we are sorry, and we thank Dr. Watson for his letter.

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Halothane Effects on Synaptosomal Acetylcholine Metabolism

To the Editor:

In the article by Johnson and Hartzell (1) concerning halothane effects on synaptosomal acetylcholine (ACh) metabolism, the 3 out of 4 reactions shown to be inhibited by 3% halothane are the same 3 out of 4 that are energy-requiring and thereby dependent on adequate intracellular energy generation. Choline transport is driven by existing transmembrane ion gradients maintained by Na, K-ATPase activity. Acetylcholine biosynthesis uses NAD^+ and ATP generated by mitochondrial oxidative phosphorylation. Finally, ACh release also requires oxidative energy, presumably for cytoplasmic free Ca^{2+} regulation (2). Studies from the laboratories of Cohen, Hunter, and others dating back almost 20 years (reviewed in reference 3) have established that

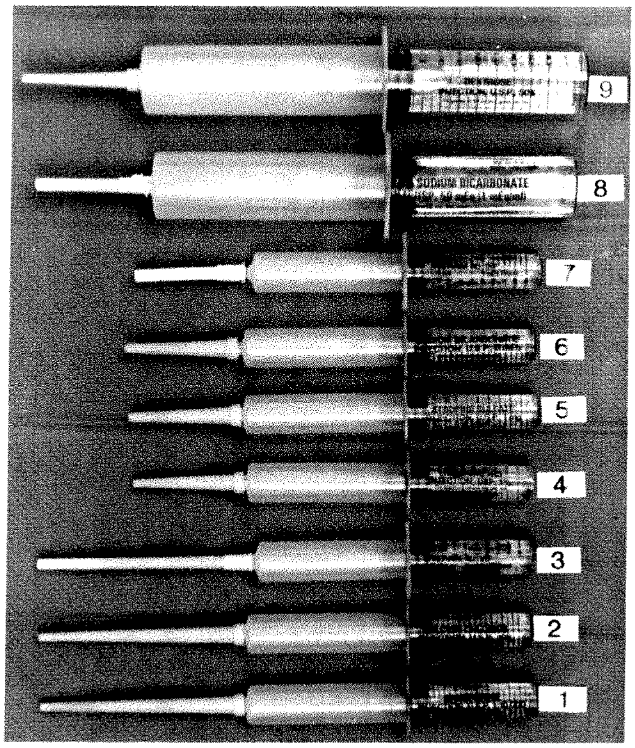

Figure 1. 1, Epinephrine, 1:10,000; 2, calcium chloride, 10%, Bristoject; 3, epinephrine, 1:10,000, Abboject; 4, lidocaine HCl, 1%; 5, atropine sulfate, 1:10,000; 6, sodium bicarbonate, 4.2%, Bristoject; 7, epinephrine, 1:10,000, Abboject; 8, sodium bicarbonate, 8.4%, Abboject; 9, dextrose, 50%, Bristoject.

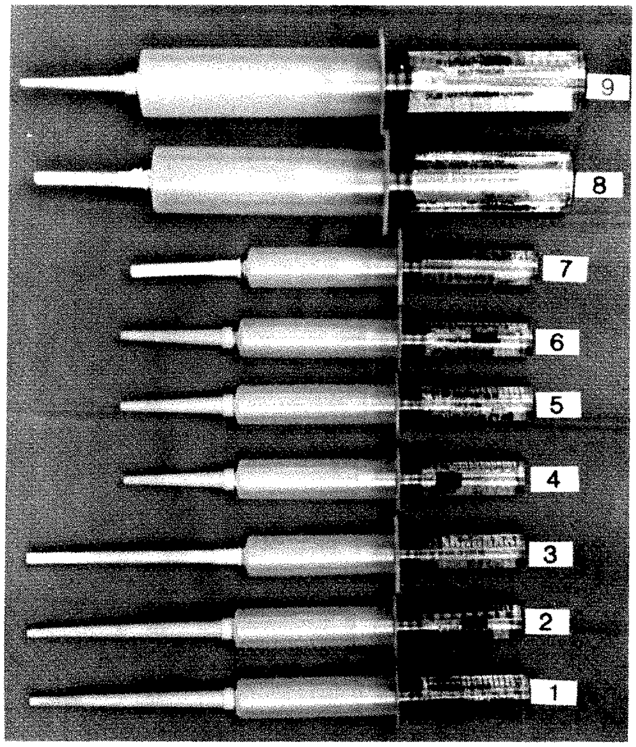

Figure 2. Syringes rolled 180°.

halothane levels as high as 3% almost completely inhibit mitochondrial energy production in vitro. In vivo, halothane concentrations exceeding 2.3% decreased cerebral high energy phosphate levels in bypass-supported dogs (4).

An alternative interpretation of the findings of Johnson and Hartzell, therefore, is that they represent direct effects of halothane on neuronal energy balance with effects on ACh metabolism being secondary to energy deficits. Such anesthetic-induced in vivo energy deficits and their secondary effects are considered to have little role in the production of anesthesia, because they are evident only at supra-MAC anesthetic concentrations (4,5).

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2. Gibson GE, Peterson C. Decreases in acetylcholine release in vitro with low oxygen. Biochem Pharmacol 1981;31:111–5.
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4. Michenfelder JD, Theye RA. In vivo toxic effects of halothane on canine cerebral metabolic pathways. Amer J Physiol 1975;229:1050–5.
5. Siesjo BK. Brain energy metabolism. New York: Wiley, 1978:256–9

Injectable Confusion[1]

To the Editor:

We read with interest the letter by Kalish (1), who noted great similarity in the packaging of nitroglycerin ointment, 2%, and lidocaine ointment, 5% (E. Fougera and Company, Division of Byk-Gulden, Inc.), and the potential risk for inadvertent misadministration of medications that this poses. A similar danger exists if single dose syringes (Abboject, Abbott Laboratories, North Chicago, IL, and Bristoject, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, NY) are removed from their packages and made ready for use (Fig. 1). Syringes 1–7 and 8 and 9 are of identical shape and size and are capped with needle covers of identical color and virtually identical shape. As the accompanying photographs show, the syringes are labeled in a manner that requires more than a casual glance to identify their contents from each another. The writing is hard to see against the clear solution and can be read in only one plane.

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[1] The opinions contained herein are those of the authors and do not necessarily reflect those of the Department of the Army or Department of Defense.

Roll a syringe 180° and the wing-shaped barrel positions the syringe so that the label is unreadable (Fig. 2).

Misadventures stemming from confusion due to the similarity in unit dose syringes have been described previously (2,3). Coding needle caps and barrel shape and size may not help to prevent error because reliance on a method to identify medications other than reading the label could be employed (4). However, manufacturers of unit dose syringes could label both syringe barrel and accompanying medication vial so the drug name would be readable in more than one plane and under less than ideal lighting conditions. Although users of unit dose syringes can minimize the risk of drug misadministration by following the manufacturer's recommendations to assemble syringes and examine labels carefully prior to use, makers of these syringes also could improve this situation by applying labels that are more readily identifiable.

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2. Freund PR, Ward RJ. Drug packaging invites confusion. Anesthesiology 1981;55:87–8.
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ANESTH ANALG
1986;65:106–9

Book Reviews

Handbook of Regional Anesthesia.

P. P. Raj, ed. NY: Churchill-Livingstone, 1985,
273 pp, $40.00.

In his preface, Dr. Raj states, "Even though presently there is a resurgence of interest in regional anesthesia, there is a definite need for a well-trained faculty to teach the techniques and for residents to perform more regional anesthesia techniques. If this need is met, the number of procedures performed utilizing regional anesthesia will increase, which in the long run will benefit the patient. I hope this book will contribute a little toward fulfilling that need."

Few will refute the resurgence of interest in regional anesthesia, the need for the discipline to be taught, or the benefits to the patient. How best to achieve these objectives is a problem that we have wrestled with long and hard. Witness the plethora of books on regional anesthesia that are now available to the resident and his teacher. Despite this, there remains no substitute for hands-on experience, and plenty of it.

Just where Dr. Raj's book falls in this panorama is subject to interpretation by the user. If he uses it as the name implies, as a "handbook of regional anesthesia," he may be well satisfied, as there is a lot of information packed into its 273 pages. However, if the user approaches it as a definitive or comprehensive text, he will come away disappointed.

The task the book assigns itself is awesome: covering the entire spectrum of regional anesthesia and its applications. In doing so the book fights against its own space limitations, and many areas are treated quite superficially or incompletely. For example, in the chapter on urologic surgery, local anesthetic agents are recommended, but nothing is mentioned with regard to dose. In fact to get any recommended doses one must refer back to the chapter on techniques. It becomes bothersome to read a discussion on a technique in one section and then move to another to get the details of the technique.

Some of the information may mislead the uninitiated, e.g., the duration of a tetracaine spinal block is cited as, "up to 3.5 hours of good quality anesthesia is provided with tetracaine." One must read closely to see that several sentences before that the author recommends the use of 1:20,000 epinephrine with hyperbaric tetracaine spinal anesthesia. Likewise, 0.75% bupivacaine is advocated without any mention of the possibility of the neurotoxicity other authors seem concerned about.

The book has many excellent pen and ink drawings, five black and white photos and eight roentgenographs. The chapter "Physiology, Pharmacology and Toxicity of Local Anesthetics" is well done. It is a concise and fairly thorough discussion of the subject matter and is a definite plus in a handbook of regional anesthesia.

I believe this text will find a place in anesthesia department libraries and will be used by the resident and staff with some background in regional anesthesia, as a refresher-type reference. The novice to regional anesthesia will find it wanting and need to go to other, more detailed, texts.

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Perioperative Cardiac Dysrhythmias: Mechanisms, Recognition, Management

John L. Atlee III, MD. Chicago:Year Book Medical
Publishers, Inc., 1985, 451 pp, $49.95.

Perioperative Cardiac Dysrhythmias is a comprehensive text that complements existing textbooks of electrocardiography. The initial chapter presents a detailed description and critique of all studies on the frequency types of arrhythmias associated with anesthesia. Two other particularly outstanding sections are the chapters on general cardiac electrophysiology, including anesthetic effects on dysrhythmias, and on cardiac pacemakers. These chapters are noteworthy for their excellent diagrams and tables, categorizing material not readily available to anesthesiologists in other works. Indeed, the tabulation of pacemakers, their responses to electromagnetic interference, possibility of reprogrammability, and changes with battery failure rivals the coverage found in a textbook of cardiac pacemakers. The chapter on pharmacologic therapy for dysrhythmias completely distinguishes both in vitro and in vivo effects of currently available and investigational new drugs.

As a single-authored text, the writing style is clear and consistent throughout, without unnecessary repetition. Extensive references are provided with each chapter, the ma-

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jority of which were published in the late 1970s or 1980s. A 44-page index allows the reader to readily locate specific topics. Misprints are infrequent. The typeface is clear and bold.

Unfortunately, the discussions of abnormal electrical activity of the heart and the surface electrocardiogram offer little new or unique information that cannot be found in standard texts of electrocardiography. Subjects such as intraoperative defibrillation and clinical electrophysiologic studies receive only limited treatment in this otherwise complete reference.

However, the significant advances in cardiac electrophysiology and the management of perioperative dysrhythmias described in this excellent text more than justify its inclusion in the libraries of the departments of anesthesiology and practitioners of cardiac anesthesia and cardiology.

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Editor's Note: The author and publisher have requested that attention be called to an error involving a dangerously wrong dosage of bretylium on page 404, table 9-2. The dosage should read 1–2 mg/min, not 1–2 mg/kg/min.

Précis D'Anesthésie Loco-Régionale

P. Gauthier-Lafaye, ed. Paris: Masson, 1985, 336 pp.

This manual on regional anesthesia techniques represents an outstanding contribution to the field. It is written in French and consists of 14 chapters which are consistently well organized and provide a comprehensive "how to" for each of the techniques described. The compilation is the work of thirteen contributors from five medical schools in France, Canada, and the United States. The chapters dealing with techniques for peripheral nerve blocks are practical in their orientation. Those dealing with epidural and spinal anesthesia, as well as the epidural and subarachnoid applications of opiates, are somewhat more theoretical in scope. Most of the chapters are extensively referenced. The art work is superb. There is an abundance of full color and black and white anatomic drawings of consistently high quality. Each of the illustrations is the work of Dr. J. Farny, who is both a clinical anesthesiologist and medical artist. The uniformity and clarity of the art make the text additionally valuable as a learning aid for even the non-French reading student. Dr. Gauthier-Lafaye is to be commended for this international contribution.

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Anesthesiology—A Manual for Medical Students

Rhoda D. Levine, ed. Philadelphia: J.B. Lippincott Company, 1984, 207 pp, $15.75.

This multi-authored text was designed as an introduction to anesthesia for medical students. The authors achieve their stated goal of introducing medical students to the concepts and skills that all physicians should know about this specialty. The text is effectively organized into four primary sections: agents and techniques, the perioperative period, patients with specific management problems, and other topics of importance to the anesthesiologist. Each chapter is short, concise, and well written. Information is delivered in a succinct manner. The diagrams and charts augment the text. Although a contributor's personal philosophy is occasionally presented, on the whole the matter presented is unbiased. The writing style is consistent, which improves the readability.

The major criticism of the text concerns the suggested readings. In approximately 25% of the chapters they are omitted. A good number are older than 10 years, and some will be difficult to find both because of age (journal will be on microfilm) and unavailability. Nowhere is there mentioned a general reference for the more interested and aggressive student to turn to. In general, this book should be a welcome addition to the medical student's bookcase—a good buy for a reasonable price.

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GASMAN—Understanding Anesthesia Uptake and Distribution.

James H. Philip. Menlo Park, CA: Addison-Wesley Publishing Co., Inc., 1984, 104 pp, $150.00.

Dr. Philip is to be congratulated for having produced a user friendly computerized introduction to the subject of the uptake of inhalation anesthetics. His illustrations of the effect of circuit volume, fresh gas flow, alveolar minute ventilation, cardiac output, anesthetic solubility in blood, anesthetic tension in mixed venous blood on the rise of anesthetic in blood, and anesthetic tension in mixed venous blood on the rise of anesthetic tension in alveolar gas and vessel rich tissues are clear. The text is well written, carefully restating the effects to be observed on the graphs and teaching one to experiment with the program as well. The presence of both graphic and pictoral formats on the computer screen may indeed engage attention more effectively than either alone could. But some may find the requirement for game paddles more a nuisance than an engaging simulation of an anesthesia machine. Sound was well used.

Perhaps the most interesting parts of this simulation are chapters 9 and 10. There one is guided into low flow and closed circuit anesthetic administration. As Dr. Philip notes, these techniques offer potential savings in wasted anesthetic gas and potential avoidance of exposure of personnel to these wastes. Because the same principles of anesthetic uptake and distribution apply no matter what the method of gas administration, it is quite logical to include these two less frequently practiced methods in this teaching tool. Here some of the benefits of low flow and closed circuit anesthetic administration are easily appreciated.

I was disappointed that I could not force the system to crash, or at least alarm, by giving increasingly large amounts of halothane. Because the cardiovascular effects of the potent inhalation anesthetics often become somewhat limiting, it would be inappropriate to leave the student with the impression that anesthetic induction with potent vapors does not alter cardiac output. (Because the program does allow easy change of parameters, the anesthetist can decide him or herself how much the cardiac output might fall and try some inductions with and without concurrent alterations in cardiac output.)

But no program written for a small computer can simulate everything one might imagine in the process of the uptake and distribution of inhalation anesthetics. Dr. Philip is quite straight-forward in chapter 11 as he describes the many things this program will not do. Despite these limitations, the simple educational value of the program is preserved. It models the most important factors affecting the movements of inhalation anesthetics from the gas source to the patient's vessel rich group of tissues. These factors are of utmost importance during the induction of inhalation anesthesia. GASMAN is useful for its illustration of these basic points in daily anesthesia practice. The flexibility of the program and the clarity of the instructions accompanying it allow both the novice and the experienced anesthetist to view their techniques of inhalation anesthesia more critically.

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The Manual of Pediatric Anesthesia

D. S. Steward. New York: Churchill Livingstone, Inc., 1984, 377 pp, $24.00.

The goals of the 2nd edition of *The Manual of Pediatric Anesthesia*, edited by Dr. David Steward, are to present the principles of pediatric anesthesia and to describe the techniques employed at the Hospital for Sick Children, Toronto. The text is divided into three sections. The first section on foundations of pediatric anesthesia provides the reader with a very good, concise summary of the psychologic, anatomic, physiologic, pathophysiologic, and pharmacologic aspects of infant and children care. This section is particularly well referenced. The second section on anesthesia for specific procedures is the heart of the manual and comprises 202 of the 377 pages of the text. The third section consists of four appendices which include a summary of the anesthetic implications of syndromes, suggested minimal stay in the postoperative recovery area, suggested drug dosages of anesthetic and adjuvant agents, and finally a review of pediatric cardiopulmonary rescusitation.

Although this reviewer believes that the authors have achieved their goals in an admirable fashion, several obvious omissions are worth noting. The intraoperative use of somatosensory evoked potentials and its application to the surgical approach for kyphoscoliosis, tethered cord, spinal cord tumors, and aortic coarctation goes unmentioned. The section on the management of the acutely burned patient (p 284) fails to recommend the insertion of a Foley catheter in order to assess fluid resuscitation, nor does it mention alterations in the serum ionized calcium concentration or the resistance to the nondepolarizing neuromuscular relaxants. Although the section on renal surgery (p 258) is excellent overall, the author fails to describe the treatment of hyperkalemia. A recommendation to consult a nephrologist is a cop-out!

In the preface (p IX), the editor states that many conditions covered within will be successfully treated only in a specialty unit. This statement appears in the only bold type within the entire text. Although this issue is clearly of significant philosophical, ethical, and practical interest to the editor, he fails to elaborate on this within in the text. This reviewer was disappointed with that omission.

In addition to omissions, there are several controversial statements made without recognition that there is a disagreement, especially for otolaryngological procedures. For example, management of the patient with laryngotracheobronchitis (croup, p 160) is hotly debated. Tracheostomy after intubation remains the most frequently chosen path, whereas maintenance with a translaryngeal airway (their recommendation) is extremely controversial. Another example is their statement that the management of laryngeal papillomatosis by tracheostomy, jet ventilation, or both is absolutely contraindicated (p 154). The distal spread of papilloma by jet technique has always been considered possible, but there has been meager clinical substantiation. In the appropriate patient jet ventilation is a safe technique when the anesthesia and surgical staff are alert to possible adverse sequellae. A statement on page 144 that cor pulmonale from chronic upper airway obstruction is associated with blacks is unsubstantiated.

The use of positive end expiratory pressure (PEEP) in neonates with congenital diaphragmatic hernia, which they recommend, is considered by most clinicians to be detrimental (p 186). PEEP increases the pulmonary airway pressure, and this increase is transmitted directly to the pulmonary vasculature. PEEP should be used only if significant pulmonary parenchymal disease coexists and the improvement of A-aDO_2 outweighs the adverse affect on the pulmonary vascularity. Finally, their statement regarding the absolute incompatability of halothane with epinephrine by infiltration is certainly worth challenging. Even the most conservative compatable dosages offer more flexibility to the surgeon and the anesthesiologist than none at all. A recent study reported the safe use of epinephrine up to 10 μg/kg in pediatric patients receiving 1 MAC of halothane (1).

This is an institutional manual, and therewithin lies its weakness. There is no room to cover the range of circumstances, opinions, and skills available at other institutions. However, this manual represents the approach of a highly respected institution and as such is a very valuable addition to any reference library.

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Reference

1. Karl HW, Swedlow DB, Lee KW, Downes JJ. Epinephrine-halothane interactions in Children. Anesthesiology 1983;58:142–5.

Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in future issues of Anesthesia and Analgesia.

Intensive Care Manual, 2nd ed. T. E. Oh. Boston: Butterworths, 1985, 463 pp, $29.95.

A Physician's Guide to Computers and Computing. J. M. Allswang, J. I. Isenberg, and M. H. Weiss. Norwalk, CT: Appleton-Century-Crofts, 1985, 208 pp, $29.95.

Pulmonary Development, Transition from Intrauterine to Extrauterine Life. Vol. 27, Lung Biology in Health and Disease Series. G. H. Nelson, ed. NY: Marcel Dekker, Inc., 1985, 536 pp, $70.00 (US and Canada), $90.00 (all other countries).

Regional Anesthesia and Clinical Applications. H. Carron, G. A. Korbon, and J. C. Rowlingson. Orlando, FL: Grune and Stratton, 1985, 1987 pp, $39.50.

A Guide for Authors

Manuscripts should be sent to:

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Editorial Policies

Anesthesia and Analgesia is the oldest publication for the specialty of anesthesiology. Established 60 years ago, the Journal is the official voice of the International Anesthesia Research Society. It publishes original articles, clinical reports, technical communications, review articles, and letters to the editor to provide researchers, practicing physicians, and allied medical personnel in anesthesiology and related disciplines with monthly information to keep them current with the latest issues and advances in the field.

All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Only one copy of the articles not accepted for publication will be returned to the author.

All papers will be edited for clarity, style, factual accuracy, internal logic, and grammar. The submitted manuscript should be accompanied by a covering letter that must include a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar, work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *Annals of Internal Medicine* 1982;96:766-71 and *Lancet* 1982;284:1766-70.

Use the checklist given below for preparation of manuscripts:

General

- ☐ Original articles describe in 3000 words or less clinical or laboratory investigations.
- ☐ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.
- ☐ Technical communications are papers that deal with instrumentation and analytic techniques.
- ☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts.
- ☐ Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be double spaced, and a title and three copies must be provided.
- ☐ Type manuscripts on white bond paper, 216 by 279 mm (8-1/2 by 11 in.) or ISO A4 (212 by 297 mm) with margins of at least 25 mm (1 in) using double spacing throughout.
- ☐ Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, should be on a separate page), and legends. Type only on one side of the paper and number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.
- ☐ Submit three copies of manuscript and figures in a heavy paper envelope. Submitted manuscripts should be accompanied by a covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.
- ☐ Authors should keep copies of everything submitted.

Title Page

- ☐ The title page should contain the title of the article, which should be concise but informative;
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- ☐ First name, middle initial, and last name of each author, with highest academic degree(s);
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Abstract and Key Words

- ☐ The second page should carry an abstract of not more than 150 words.
- ☐ The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals; observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations.
- ☐ Define all abbreviations except those approved by the International System of Units.
- ☐ Key (indexing) terms: Below the abstract, provide (and identify as such) 3 to 10 key words or short phrases that will assist indexers in cross indexing the article and that may be published with the abstract.

Text

- ☐ The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially in the Results and Discussion sections.
- ☐ Case reports, reviews, and editorials do not require the above sections.
- ☐ *Introduction:* Clearly state the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.
- ☐ *Methods:* Describe the selection of observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.
- ☐ Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration.
- ☐ Do not use patients' names, initials, or hospital numbers.
- ☐ Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

- ☐ *Results:* Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.
- ☐ *Discussion:* Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not completely supported by the data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such.
- ☐ Recommendations, when appropriate, may be included.

References

- ☐ Number references consecutively in the order in which they are first mentioned in the text, except in review articles when references may be arranged alphabetically.
- ☐ Identify references in text, tables, and legends by arabic numerals (in parentheses, on line).
- ☐ Use the style of the examples below, which are based on the format used by the US National Library of Medicine in *Index Medicus.*
- ☐ The titles of journals must be abbreviated according to the style used in *Index Medicus.*
- ☐ Try to avoid using abstracts as references; "unpublished observations" and "personal communications" may not be used as references although references to written, not verbal, communications may be inserted (in parentheses) in the text. Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses). Authors citing as references articles from their own group that are in press and that have a bearing on the paper submitted should enclose 3 copies of an abstract of such in press materials.
- ☐ References must be verified by the author(s) against the original documents.
- ☐ Examples of correct forms of references are given below:

Journals:

1. *Standard Journal Articles* (List all the authors when six or less; when seven or more, list only the first three and add et al.)
   You CH, Lee KY, Chey RY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroenterology 1980;79:311–4.
2. *Corporate Author*
   The Royal Marsden Hospital Bone-Marrow Transplantation Team. Failure of syngeneic bone-marrow graft without preconditioning in post-hepatitis marrow aplasia. Lancet 1977;2: 242–4.
3. *No Author Given*
   Anonymous. Coffee drinking and cancer of the pancreas (Editorial). Br Med J 1981;283:628.
4. *Journal Supplement*
   Mastri AR. Neuropathy of diabetic neurogenic bladder. Ann Intern Med 1980;92(2 Pt 2):316–8.

   Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan (Abstract). Blood 1979;54(suppl 1):26a.
5. *Journal Paginated by Issue*
   Seaman WB. The case of the pancreatic pseudocyst. Hosp Pract 1981;16(Sep):24–5.

Books and Other Monographs:

6. *Personal Author(s)*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
7. *Editor, Compiler, Chairman as Author*
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12. *Dissertation or Thesis*
    Cairns RB. Infrared spectroscopic studies of solid oxygen (Dissertation). Berkeley, California: University of California, 1965. 156 pp.

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☐ Consult the following sources for abbreviations:

1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington, Virginia: Council of Biology Editors, 1978; and
2. O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam: Elsevier-Excerpta Medica, 1975.

Ethical Principles

☐ When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or are in accord with the Helsinki Declaration of 1975.

☐ When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed.

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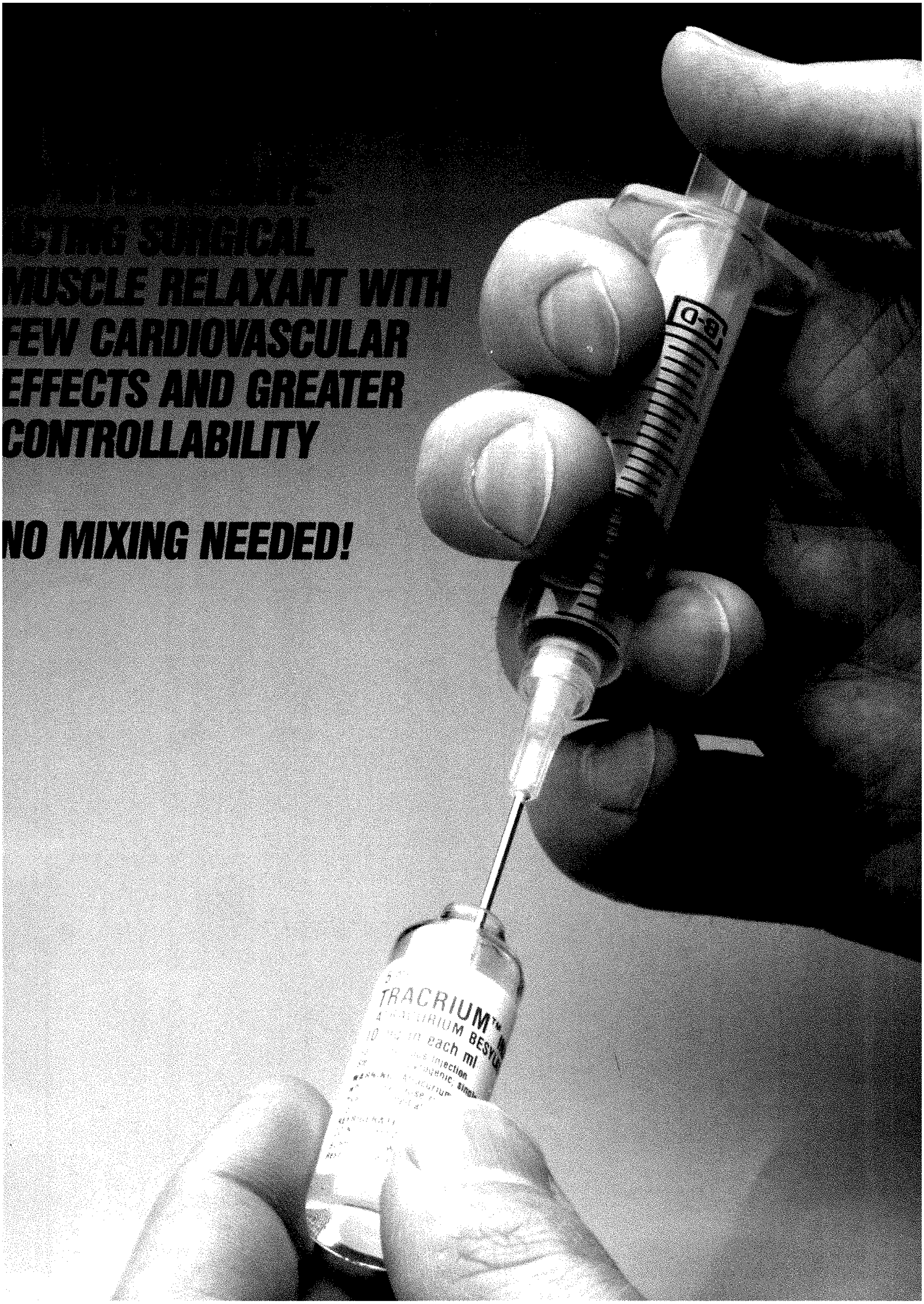
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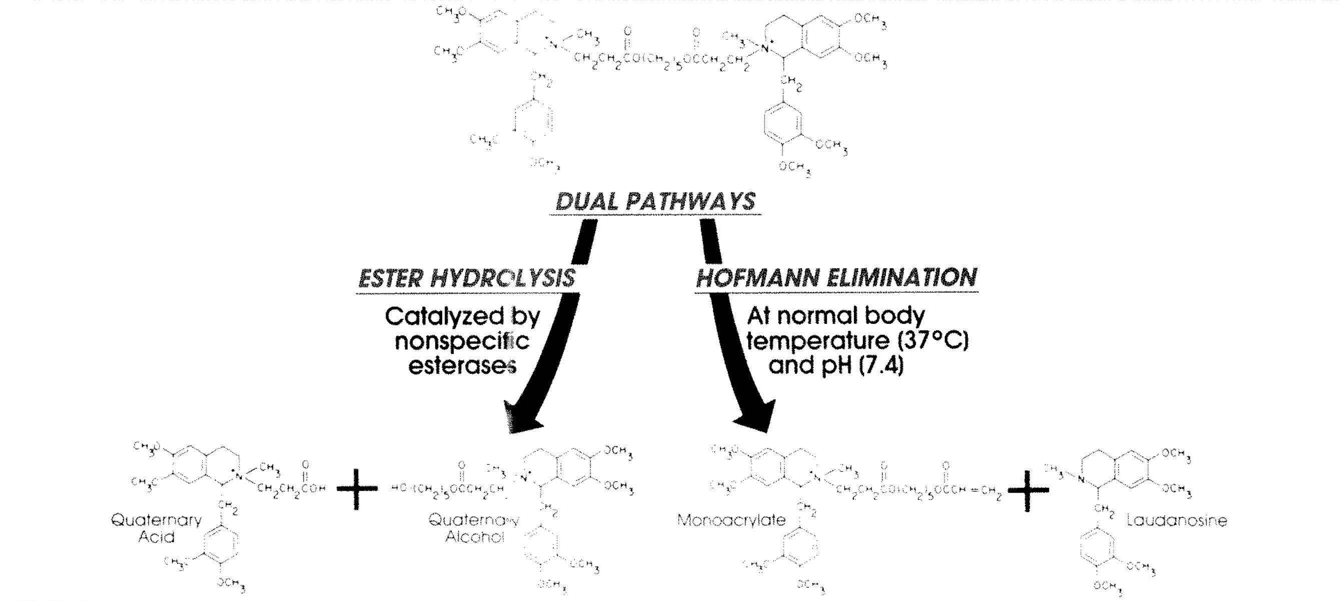


☐ *Tracrium* Injection (atracurium besylate) is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:*

1 *Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH*

2 *Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required*

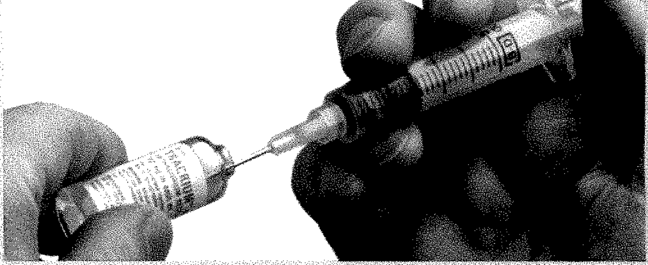
These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."[1]

"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."[2]

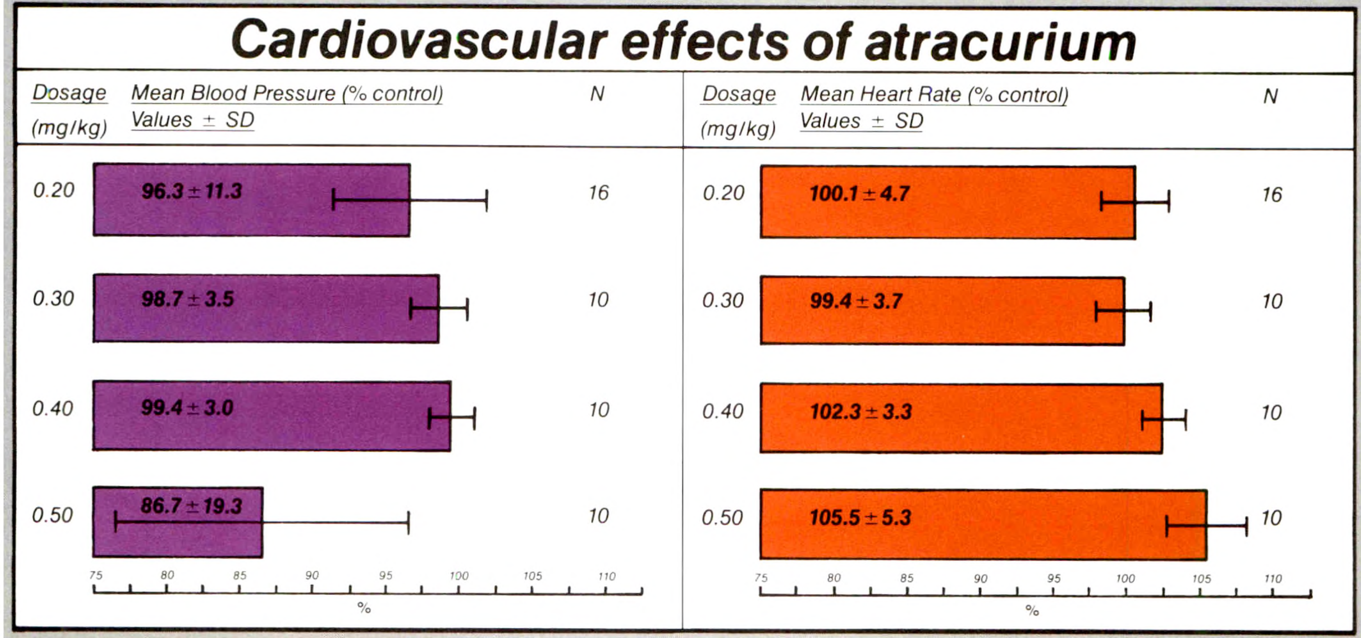
Convenient and Ready to Use

Tracrium is easily administered—requires no premixing.



Few Cardiovascular Effects at Recommended Dosages

☐ Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.



Adapted from Basta et al.[3]

No Cumulative Effects Upon Recovery, After Multiple Doses

☐ Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time

☐ Once recovery begins, it is relatively rapid and independent of dose

☐ This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."[1]

Minimal Histamine Release

☐ Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine

☐ Clinically significant histamine release occurs well within the clinical dosage range (at ED_{95}) for curare, at the upper limits of the clinical dosage range (at 2 × ED_{95}) for metocurine and outside the clinical dosage range (at 3 × ED_{95}) for atracurium[4]

☐ The lack of hemodynamic changes due to Tracrium suggests minimal histamine release

Please see brief summary of prescribing information on the following page.

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TRACRIUM® INJECTION
(atracurium besylate)

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TRACRIUM® INJECTION
(atracurium besylate)

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

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Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower, concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 2 years have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:
Musculoskeletal: Inadequate block, prolonged block
Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia
Respiratory: Dyspnea, bronchospasm, laryngospasm
Integumentary: Rash, urticaria, reaction at injection site

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

HOW SUPPLIED: Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).

10 ml Multiple Dose Vial (100 mg atracurium besylate per vial). The multiple dose vial contains 0.9% benzyl alcohol added as a preservative. Box of 10 (NDC-0081-0940-95).

Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

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Down the hall, Dr. Jones had a marathon case involving a young woman undergoing a tuboplasty for infertility. Finally, 5½ hours later the surgeons were closing the skin. He heaved a sigh of relief and automatically leveled the table from the previous several hours where the Trendelenberg position had been necessary.

But these two stories don't end here. About 28 days later, *both patients had a bald spot about the size of a silver dollar at the occiput. . . exactly where their heads were resting on the table for hours on end.* They were each advised by their surgeons that they had a 50% chance of their hair growing back within the next year. But there was an equal chance that their hair wouldn't grow back at all. The anesthesiologists on both cases were never told of the problem.

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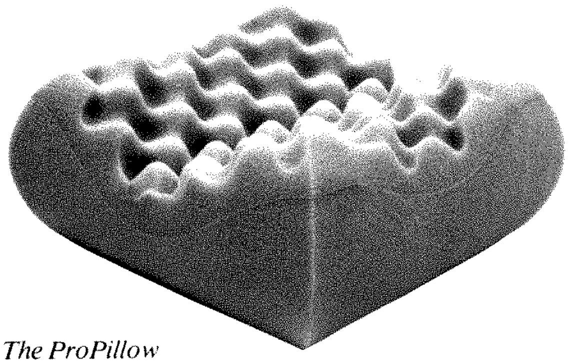

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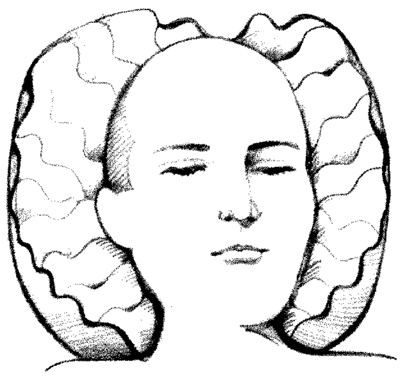

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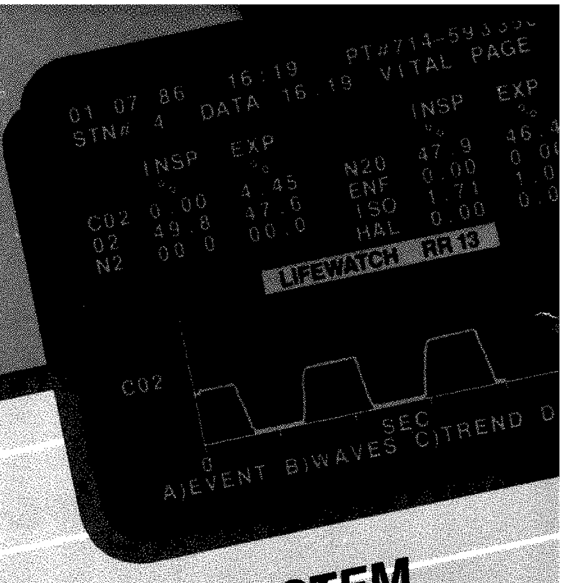

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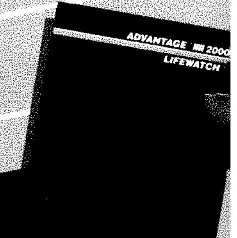

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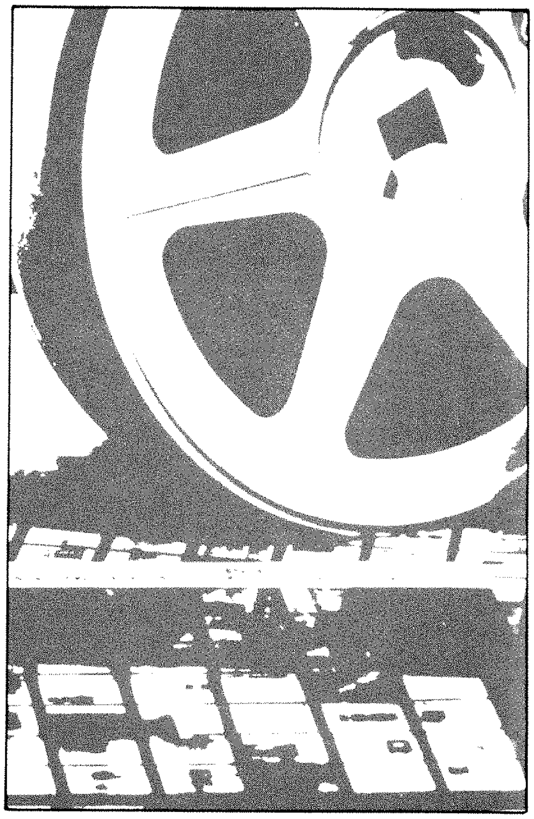

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Volume 65, Number 2, February 1986

Anesthesia and Analgesia

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In

Reversal

of nondepolarizing
muscle relaxants,
don't look for what's better...
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Regonol®

(pyridostigmine
bromide injection, USP)
when compared to neostigmine

☐ Clinically fewer side effects
☐ Significantly lower degree and incidence of:
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BRIEF SUMMARY—(Please consult full package insert, enclosed in every package, before using Regonol)

INDICATIONS—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

CONTRAINDICATIONS—Known hypersensitivity to anticholinesterase agents: intestinal and urinary obstructions of mechanical type.

WARNINGS—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg./kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

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REFERENCES:

1. Gyermek L: Clinical studies on the reversal of the neuromuscular blockade produced by pancuronium bromide. 1. The effects of glycopyrrolate and pyridostigmine *Curr Ther Res* 18:377-386, 1975.
2. Ravin MB: Pyridostigmine as an antagonist of d-tubocuranrine-induced and pancuronium-induced neuromuscular blockade. *Anesth Analg—Curr Res* 54:317-321, 1975.

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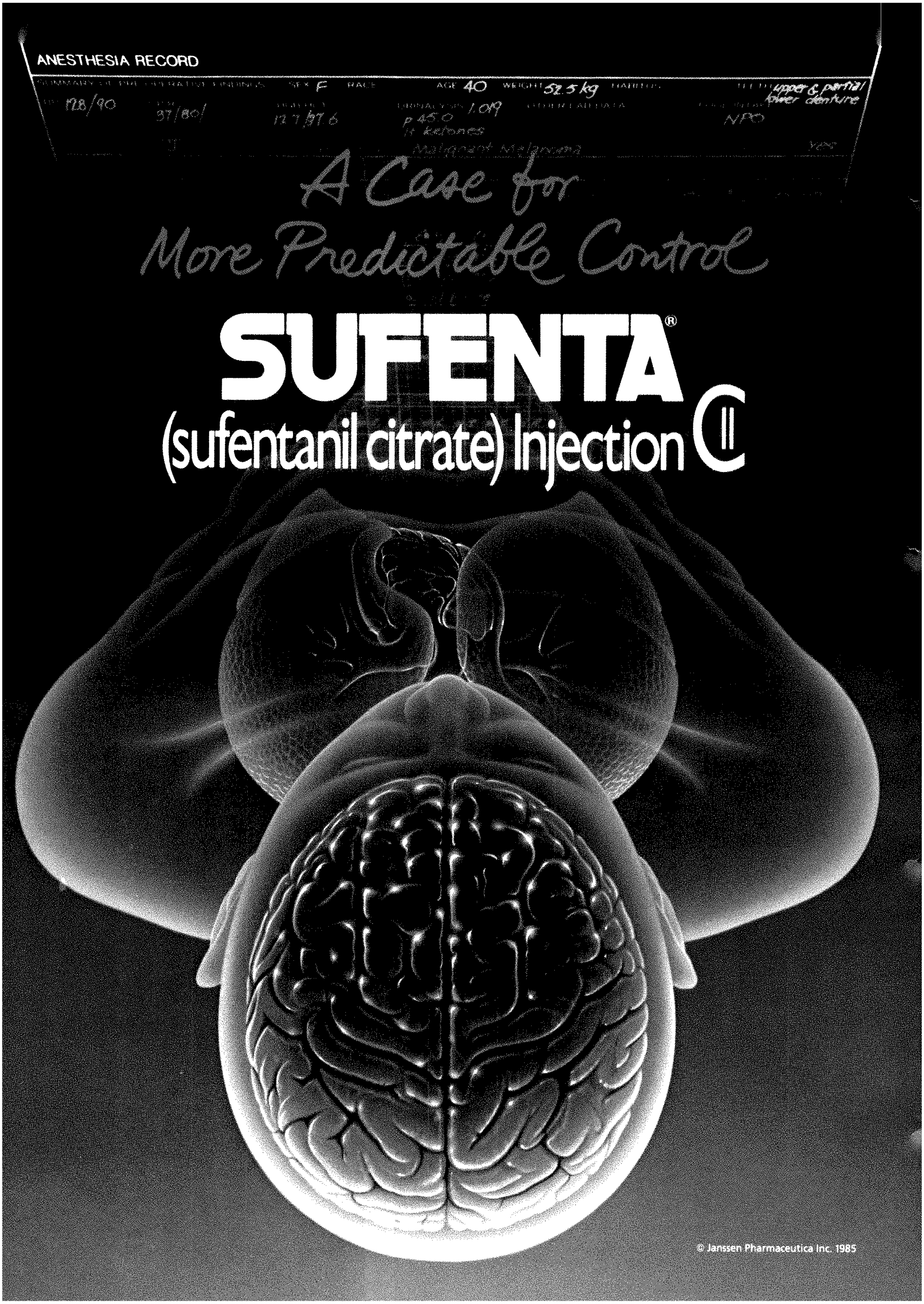

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SUMMARY OF PRE-OPERATIVE FINDINGS SEX F RACE AGE 40 WEIGHT 52.5 kg HABITUS TEETH upper & partial lower denture

128/90 97/80/ 12.7/37.6 URINALYSIS 1.019 p 45.0 1+ ketones OTHER LAB DATA NPO

Malignant Melanoma Yes

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1. Scientific Exhibit, Sufentanil vs. Isoflurane in Major Orthopedic Procedures (Fahmy NR, Principal Investigator), March 1983.

2. Fahmy NR, Beemer GH, Roberts JT: Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

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3. Smith NT, Dec-Silver H, Harrison WK, et al: ASA Abstract, Anesthesiology (Suppl) 57: A291, 1982.
4. Flacke JW, Bloor BC, Flacke WE, et al: Comparative Effects of Sufentanil and Fentanyl Versus Meperidine and Morphine in Balanced Anesthesia. Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

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SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 μg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-7.5.

CLINICAL PHARMACOLOGY

SUFENTA is an opioid analgesic. When used in balanced general anesthesia, SUFENTA has been reported to be as much as 10 times as potent as fentanyl. When administered as a primary anesthetic agent with 100% oxygen, SUFENTA is approximately 5 to 7 times as potent as fentanyl. (See dosage chart for more complete information on the use of SUFENTA). At doses of up to 8 μg/kg, SUFENTA provides profound analgesia; at doses ≥8 μg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 1.4 minutes, redistribution of 17.1 minutes and an elimination half-life of 164 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with equipotent dosages of fentanyl. At dosages of SUFENTA of 1-2μg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 μg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 μg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 μg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 μg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 μg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 μg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA produced EEG patterns and reductions in cerebral blood flow and oxygen utilization comparable to those of enflurane.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Skeletal muscle rigidity is related to the dose and speed of administration of SUFENTA. This muscular rigidity may occur unless preventative measures are taken (see Warnings).

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated:

as an analgesic adjunct in the maintenance of balanced general anesthesia.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS

SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 μg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 μg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 μg/kg).

The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS

General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE

SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE

Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION

The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 μg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 μg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

Usage in Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 μg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 μg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART

TOTAL DOSAGE	MAINTENANCE DOSAGE
ADMINISTRATION WITH NITROUS OXIDE/OXYGEN FOR SURGICAL PROCEDURES LASTING UP TO EIGHT HOURS: **● TOTAL DOSAGE REQUIREMENTS OF 1 μG/KG/HR OR LESS ARE RECOMMENDED**	
1-2 μg/kg: Expected duration of anesthesia 1-2 hours. Approximately 75% or more of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	**10-25 μg (0.2-0.5 ml):** as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to remaining operative time anticipated.
2-8 μg/kg: Expected duration of anesthesia 2-8 hours. Approximately 50 to 75% of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	**10-50 μg (0.2-1 ml):** as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
ADMINISTRATION WITH 100% OXYGEN	
8-30 μg/kg: (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 μg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 μg/kg, catecholamine release is attenuated. Dosages of 25-30 μg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	**25-50 μg (0.5-1 ml):** as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of SUFENTA accurately, the use of a tuberculin syringe or equivalent is recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

NDC 50458-050-01	50 μg/ml, 1 ml ampoules in packages of 10
NDC 50458-050-02	50 μg/ml, 2 ml ampoules in packages of 10
NDC 50458-050-05	50 μg/ml, 5 ml ampoules in packages of 10

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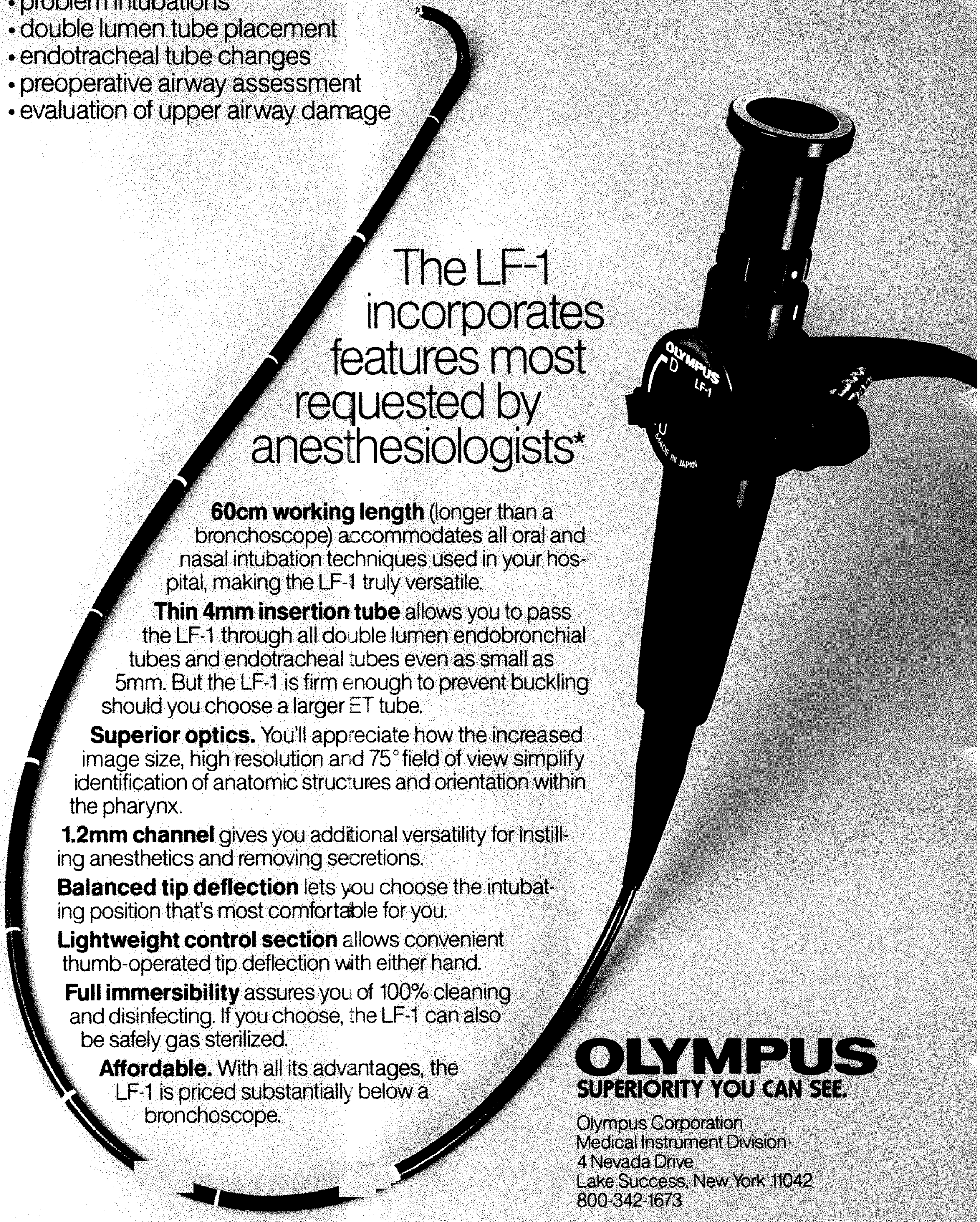

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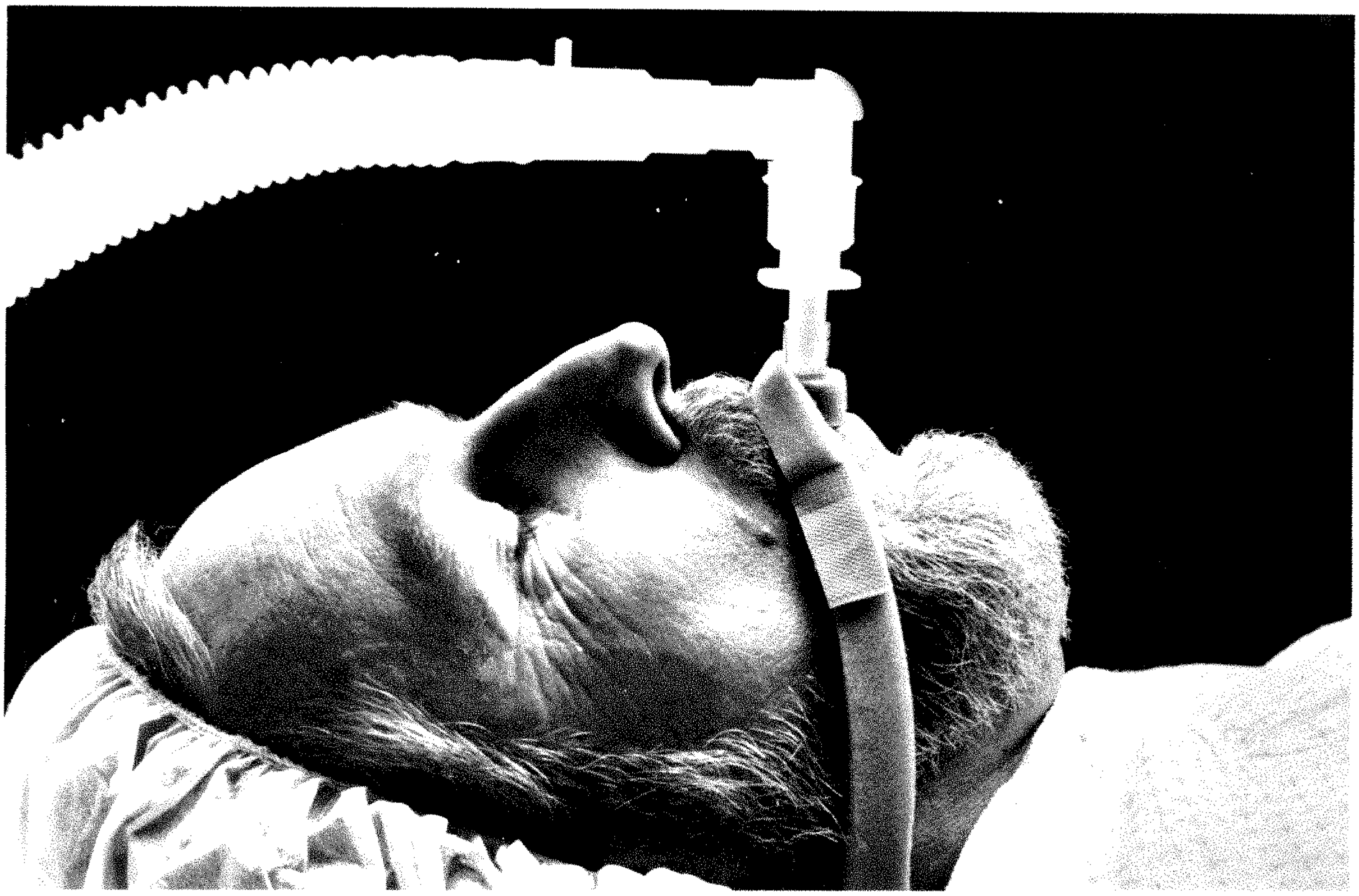

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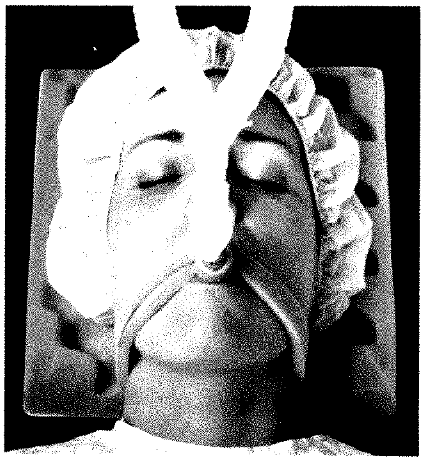

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Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,[1-3] and hemorrhagic, traumatic, or septic shock.[4,5,7]

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Please see references and brief summary of prescribing information on following page

References: 1. Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg 34* (6):674-679, 1982. 2. Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med 11* (12):943-945, 1983. 3. Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg 37* (1):40-46, 1984. 4. Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med 9* (12):833-837, 1981. 5. Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg 118*:804-809, 1983. 6. Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion 22* (3):226-228, 1982. 7. Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med 11*(11):839-850, 1983.

HESPAN® (hetastarch)

6% Hetastarch in 0.9% Sodium Chloride Injection

CONTRAINDICATIONS

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

WARNINGS

Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

Usage in Children: No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

PRECAUTIONS

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

ADVERSE REACTIONS

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

HOW SUPPLIED

NDC **0094-0037-05-Hespan®** (6% Hetastarch in 0.9% Sodium Chloride Injection) is supplied sterile and nonpyrogenic in 500 ml intravenous infusion bottles.

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EXPERT4 offers a spreadsheet which enables the user to create files or 'domains' each of which is made up of 'elements' which have 'attributes'. These have 'attribute values'. For example, in a domain called 'People', 'Jane' is an element. One of her attributes is 'Hair colour'. Jane has brown hair hence 'Brown' is the attribute value.

Inferencing facilities in EXPERT4 calculate and display relationships amongst the elements and attributes in terms of similarity and typicality. Any two selected items can be compared in detail for their similarities and differences.

An example use would be to assist with diagnosis of a group of diseases with similar symptoms. Existing knowledge of the diseases can easily and quickly be entered into a domain and new information is easily incorporated later. Similarities and differences between items can be explored in terms of the high-level concepts physicians usually employ.

EXPERT4 offers facilities for manually constructing decision tree rules. Decision rules are used in expert systems to enable users to classify new items (e.g. diagnose new cases) while minimising the requests for information about the item. EXPERT4 supports facilities for selecting sub-sets of items. All calculations can be performed on sub-sets as well as the whole domain.

Thus a flexible diagnostic tool is created which can quickly distinguish whether a patient's symptoms are more typical of diagnosis A than diagnosis B, C or D.

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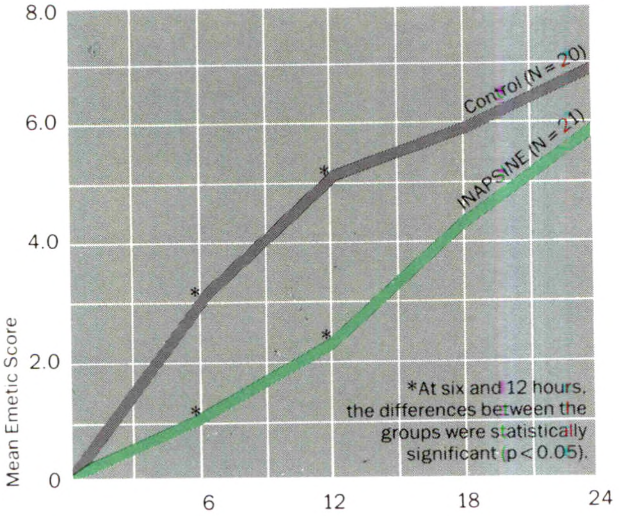
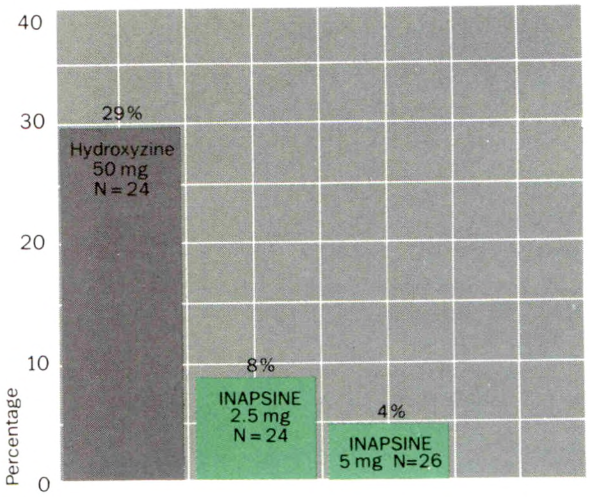
Double-blind study of 41 patients undergoing hysterectomy. Twenty-one patients received 5 mg INAPSINE shortly after surgery began, while 20 patients received placebo. Postoperative emesis was rated according to an emetic scoring system Patients receiving INAPSINE had significantly less frequent and less severe nausea, retching and vomiting during the first 12 postoperative hours.

INAPSINE vs placebo: mean total emetic scores. The lower the score, the fewer and less severe the incidents of emesis. (Adapted from Patton CM Jr, Moon MR, Dannemiller FJ[1])



Double-blind comparison of INAPSINE 5 mg, INAPSINE 2.5 mg and hydroxyzine 50 mg, combined with meperidine or morphine and glycopyrrolate, as premedication in 74 women undergoing major elective gynecologic surgery. Significantly fewer of the patients receiving INAPSINE experienced postoperative nausea/vomiting than those receiving hydroxyzine ($p < 0.05$).

Percentage of patients experiencing postoperative nausea/vomiting according to premedication ($p < 0.05$). (Based on Mehta P, Theriot E, Mehrotra D, et al[2])



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NDICATIONS: INAPSINE (droperidol) is indicated: • to produce anquilization and to reduce the incidence of nausea and vomiting surgical and diagnostic procedures; • for premedication, induction, and as an adjunct in the maintenance of general and regional nesthesia; • in neuroleptanalgesia in which INAPSINE (droperidol) given concurrently with a narcotic analgesic, such as SUBLIMAZE* entanyl) injection, to aid in producing tranquility and decreasing nxiety and pain.
CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated patients with known intolerance to the drug.
WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE.
As with other CNS depressant drugs, patients who have received NAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic uch as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination s used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.
PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be

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References:

① Patton CM Jr, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. *Anesth Analg* 1974;53:361-364.

② Mehta P, Theriot E, Mehrotra D, et al: Comparative evaluation of preanesthetic medications. *Cur Ther Res* 1984;35:715-720.

found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

ADVERSE REACTION: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated, respiratory arrest could occur.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia

Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.

Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

If INNOVAR* injection is administered in addition to INAPSIN (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Inser for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 m 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

How Supplied: *2 ml. and 5 ml. ampoules*—packages of 10; *10 ml. multiple-dose vials*—packages of 10.

U.S. Patent No. 3,161,645

NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10

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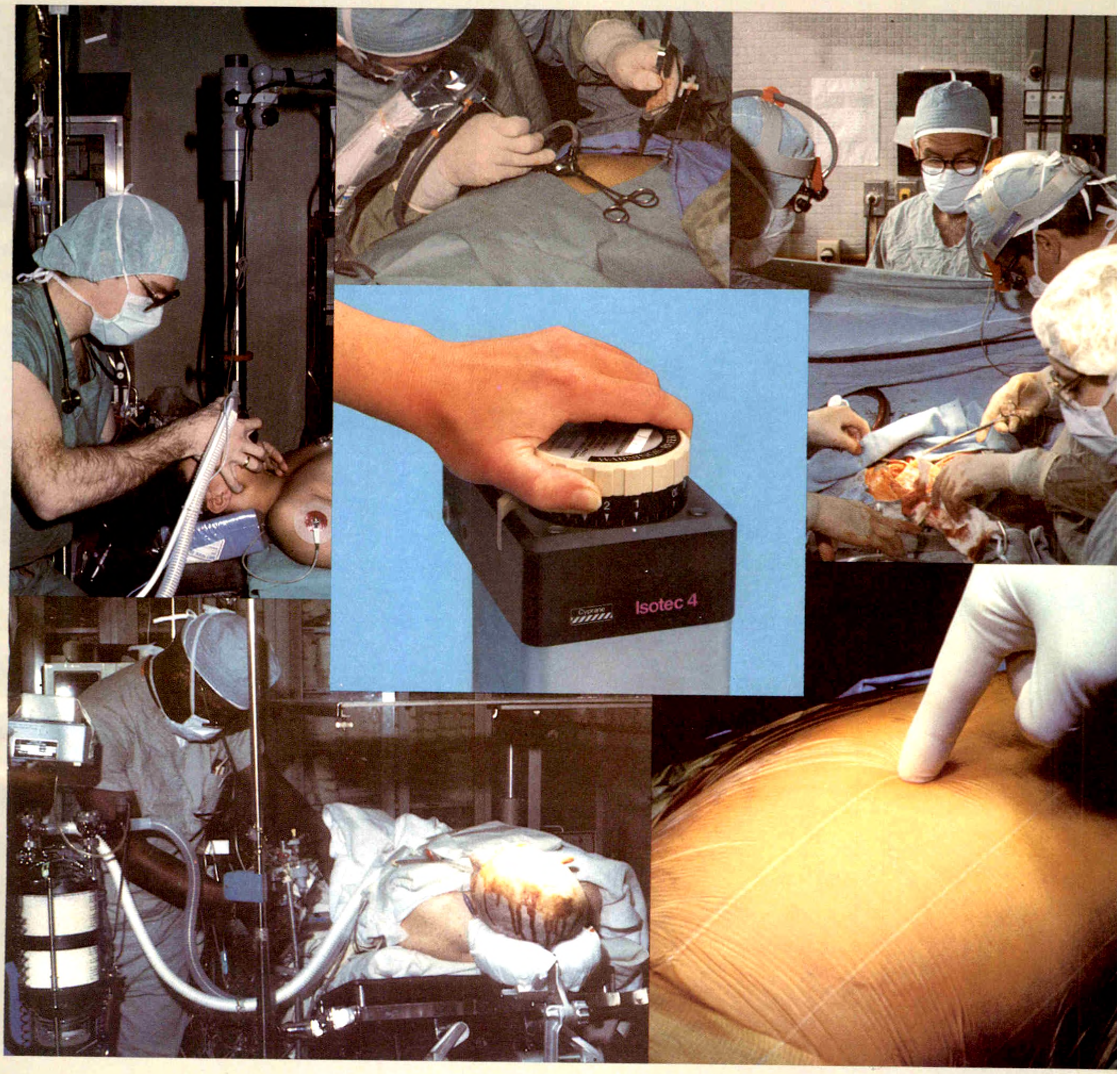

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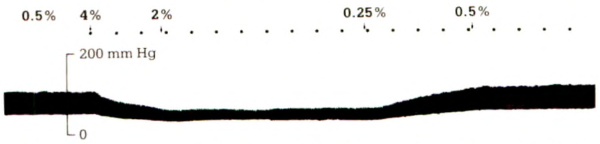
A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.[1]



Blood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.[1]

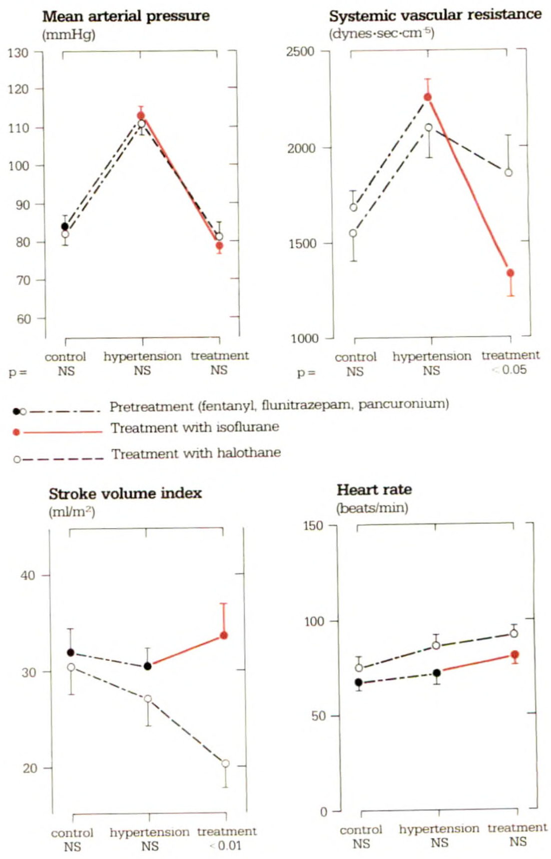
Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when $PaCO_2$ is controlled at 25-30 torr, and ICP may be readily lowered *during surgery* by decreasing $PaCO_2$.[2]

Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surger (Adapted from Hess et al[3]).



Potentiation of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).[4,5] Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."[6]

A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."[7] (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.[8]

Post-laparoscopy Nausea (N) and Vomiting (V)

Group	No. of Patients	No. of Patients with N or N&V
fentanyl, N_2O, O_2	37	23 (62%)*
isoflurane, fentanyl, O_2	20	6 (30%)
isoflurane, O_2	20	5 (25%)

Adapted from Alexander et al[8] *$p<0.05$

References:

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742-748, 1983.
2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 54:97-99, 1981.
3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. Anesth Analg 62:15-20, 1983.
4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509-514, 1971.
5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709.
6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? Anesth Analg 60(9):666-682, 1981.
7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981.
8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. Anesth Analg 63:175, 1984.

For complete use information, please see following page.

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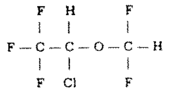
DESCRIPTION: FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$\mathrm{F-\overset{\displaystyle F}{\underset{\displaystyle F}{C}}-\overset{\displaystyle H}{\underset{\displaystyle Cl}{C}}-O-\overset{\displaystyle F}{\underset{\displaystyle F}{C}}-H}$$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where:} \quad A = 8.056,\ B = -1664.58,\ T = {}^{\circ}C + 273.16\ \text{(Kelvin)}$$

Partition coefficients at 37 °C		
Water/gas		0.61
Blood/gas		1.43
Oil/gas		90.8
Partition coefficients at 25 °C - rubber and plastic		
Conductive rubber/gas		62.0
Butyl rubber/gas		75.0
Polyvinyl chloride/gas		110.0
Polyethylene/gas		~2.0
Polyurethane/gas		~1.4
Polyolefin/gas		~1.1
Butyl acetate/gas		~2.5
Purity by gas chromatography		>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None	
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthesia.	

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY: FORANE (isoflurane) is an inhalation anesthetic The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE: FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS: Known sensitivity to FORANE (isoflurane) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS: Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS: General: As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O. See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS: Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION: Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\, P_V\, F_V}{F_T\, (P_A - P_V)}$$

where: P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED: FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0117 Revised 5-84

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Effects of Diazepam and Midazolam on Baroreflex Control of Heart Rate and on Sympathetic Activity in Humans

Jean Marty, MD, Remy Gauzit, MD, Pascale Lefevre, MD, Emmanuel Couderc, MD, Robert Farinotti, PhD, Catherine Henzel, and Jean Marie Desmonts, MD

MARTY J, GAUZIT R, LEFEVRE P, COUDERC E, FARINOTTI R, HENZEL C, DESMONTS JM. Effects of diazepam and midazolam on baroreflex control of heart rate and on sympathetic activity in humans. Anesth Analg 1986;65:113–9.

The effects of induction of anesthesia with diazepam and midazolam on baroreflex control of heart rate and on plasma levels of catecholamines were investigated in this study. Group 1 subjects (n = 10) received diazepam, 0.4 mg/kg. Group 2 subjects (n = 10) received midazolam, 0.3 mg/kg. Baroreflex function was assessed using a pressor test (phenylephrine). In addition, samples for subsequent determination of plasma norepinephrine and epinephrine levels and plasma diazepam or midazolam concentrations were collected before and 5, 10, and 15 min after intravenous drug administration. The pressor baroreflex slope declined significantly after diazepam or midazolam administration with the maximal changes (−45 and −43%, respectively) observed when plasma diazepam or midazolam concentrations were the highest. Norepinephrine plasma concentrations decreased at each measurement with both drugs. In contrast, epinephrine concentration decreased only after midazolam. The authors conclude that diazepam or midazolam used for induction of anesthesia results in a transient depression of baroreflex function and a sustained decrease of sympathetic tone. This study also indicates that the depression of arterial baroreflex heart rate responses under diazepam or midazolam anesthesia are less pronounced than the depression of baroreflex responses reported by other investigators with potent inhalational anesthetics. However, this disruptive effect of diazepam and midazolam on sympathetic control of circulation might induce a limited ability to compensate for hemodynamic alterations related to hypovolemia.

Key Words: ANESTHETICS, INTRAVENOUS—diazepam, midazolam. SYMPATHETIC NERVOUS SYSTEM—catecholamines, norepinephrine, epinephrine. REFLEXES—baroreceptors.

Hemodynamic alterations induced by anesthetic agents are mediated, in part, through their effects on the sympathetic nervous system. Most general anesthetics decrease sympathetic activity (1–3) and depress baroreflex mediated heart rate responses in humans (4–10) and animals (10–12). This disruptive effect of anesthesia on sympathetic control of circulation may be deleterious in certain clinical situations, i.e., hypovolemia and heart failure, in which sustained adrenergic activity is needed to maintain cardiovascular homeostasis (13). Because of their mild cardiovascular effects (14,15), diazepam and midazolam are widely used in the anesthetic management of critically ill patients with cardiac disease (16). However, when used after morphine in patients undergoing myocardial revascularization, diazepam exacerbates the hypotensive effects produced by morphine and is associated with decreased levels of plasma catecholamines (17). Data regarding the effects of diazepam on central autonomic reflexes in animals and humans are conflicting (18–20). Inhibition of reflex vagal bradycardia has been reported in cats (19), whereas no alteration of baroreflex response was observed 30 min after administration of low doses of diazepam in patients with heart disease (20). No information concerning the effects of midazolam on baroreflex is available. In this report, we present the findings of two investigations regarding the time-course effects of diazepam and midazolam used alone for induction of anesthesia, on baroreflex control of heart rate, and on plasma catecholamine levels in humans.

Material and Methods

Patient Selection and Groups

Twenty unpremedicated ASA class I subjects were studied before scheduled surgical procedure. Institutional approval was obtained, and all patients gave

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Table 1. Hemodynamic Data and Blood Gas Tensions (mean ± SEM): Group 1—Diazepam

	Baseline	5 min	10 min	15 min
Systolic arterial pressure (mm Hg)	129 ± 7	114 ± 4^a	112 ± 4^a	115 ± 5^a
Diastolic arterial pressure (mm Hg)	60 ± 3	55 ± 4	54 ± 4	56 ± 4
Heart rate (beats/min)	79 ± 4	78 ± 4	78 ± 3	74 ± 3
pHa	7.41 ± 0.01	7.37 ± 0.01^b	7.37 ± 0.01^b	7.37 ± 0.01^b
Pa_{O_2} (torr)	108 ± 6	94 ± 6^a	99 ± 6	102 ± 4
Pa_{CO_2} (torr)	35 ± 1	40 ± 1^b	40 ± 1^b	40 ± 1^b

$^a P < 0.05$. $^b P < 0.01$ vs baseline value.

Table 2. Hemodynamic Data and Blood Gas Tensions (mean ± SEM): Group 2—Midazolam

	Baseline	5 min	10 min	15 min
Systolic arterial pressure (mm Hg)	142 ± 4	117 ± 5^a	117 ± 8^a	120 ± 7^a
Diastolic arterial pressure (mm Hg)	77 ± 3	69 ± 3^b	67 ± 5^b	66 ± 6^b
Heart rate (beats/min)	82 ± 5	84 ± 6	87 ± 5	77 ± 4
pHa	7.39 ± 0.01	7.34 ± 0.02^b	7.33 ± 0.02^b	7.32 ± 0.02^b
Pa_{O_2} (torr)	150 ± 11	150 ± 11	155 ± 12	155 ± 12
Pa_{CO_2} (torr)	38 ± 1	45 ± 53^b	46 ± 3^b	46 ± 3^b

$^a P < 0.05$. $^b P < 0.01$ vs baseline value.

informed consent. The first ten patients (5 male, 5 female), group 1, received diazepam, 0.4 mg/kg. Age ranged from 19 to 45 yr (mean 28) and mean body weight was 70 ± 4 kg (SD). The next ten patients (6 male, 4 female), group 2, received midazolam, 0.3 mg/kg. Age ranged from 25 to 58 yr (mean 43) and mean body weight was 72 ± 4 kg (SD).

Protocol

Upon the patient's arrival in the operating room, a catheter was placed into the radial artery under lidocaine local anesthesia. Thus arterial blood pressure could be measured with a Statham pressure transducer and recorded simultaneously with ECG on an Elema four-channel recorder (Mingograph). The sensitivity of baroreflex control of heart rate was assessed by increasing the blood pressure from its resting value by a small intravenous bolus of phenylephrine (pressor test). The dose selected (50–100 μg) produced an increase in systolic blood pressure of approximately 20–30 mm Hg. The blood pressure returned to preinjection level within 3 min after each dose of phenylephrine. The relationship between the value of systolic blood pressure and the succeeding R–R interval was quantitatively evaluated during the increasing phase of arterial pressure. Values of systolic pressure and R–R interval were plotted on a beat-to-beat analysis. Data were assessed by using least-square linear regression analysis of the linear part of the relation between blood pressure and R–R interval. Only patients in whom the regression slopes had a correlation coefficient greater than 0.7 were included in the group mean (nine in each group). The slope of this linear regression expressed in msec per mm Hg was used as an index of baroreflex function, as previously reported (21). In addition the pulse interval at reference arterial pressure was calculated as described by Bristow et al. (4). Before each measurement of baroreflex function, blood samples were collected from the radial catheter for subsequent measurements of plasma norepinephine and epinephrine concentrations using high pressure liquid chromatography (22); of plasma diazepam or midazolam concentration using gas chromatography; and of arterial blood gas tensions with an ABL II blood gas analyzer. Baseline measurements were performed in each patient 15 min after insertion of the radial artery and the venous catheters to allow heart rate and blood pressure to return to stable rest levels. Then, an intravenous bolus of diazepam (group 1) or midazolam (group 2) was administered. Measurements were repeated 5, 10, and 15 min after drug injection. All data were collected while patients breathed room air enriched with nasal oxygen (0.5–2 L/min).

Data Analysis

Statistical analysis was performed using an Apple IIe computer. All reported values are means ± SEM. Differences between postinjection data and baseline values were examined in each group, using analysis of variance with the Bonferroni method for paired comparison. The relation between baseline norepineph-

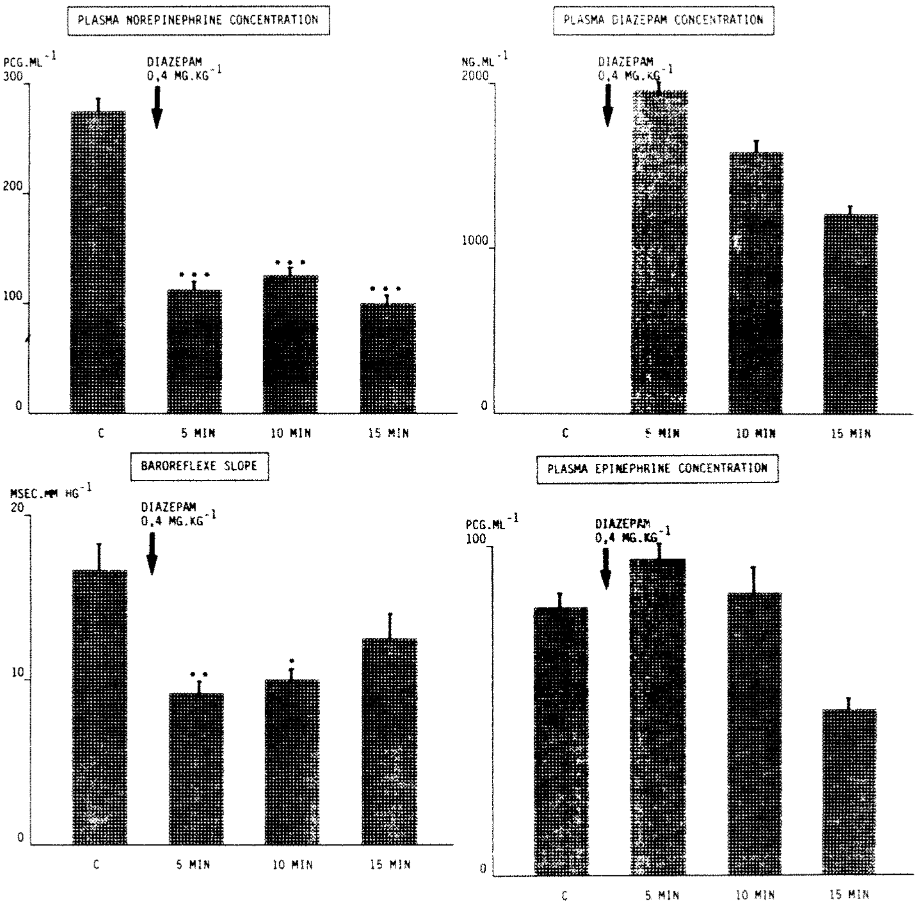

Figure 1. Baroreflex slope, plasma norepinephrine and epinephrine concentrations, and plasma diazepam concentration (mean ± SEM) plotted against time at each time of the study. Abbreviations: C, baseline period; others, see text; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ vs C.

rine concentration and the mean decrease after drug administration was analyzed in each group using least squares linear regression. No intergroup comparison was performed because administration of either diazepam or midazolam was not randomized. Statistical significance was considered at $P < 0.05$.

Results

Baseline values of blood pressure, heart rate, plasma catecholamines, slope of baroreflex function, and blood gas tensions were within normal ranges in the two groups (Tables 1, 2, Figs. 1,2). Loss of consciousness was observed in all cases within 3 min after diazepam or midazolam. The baroreflex slope decreased significantly 5 and 10 min after diazepam administration, whereas it was significantly below baseline at each measurement after midazolam injection. In the two groups, maximal changes (− 45 and − 43%, respectively) were observed at the time of the highest measured plasma diazepam or midazolam concentration, 5 min after injection (Figs. 1,2). Pulse interval at reference pressure increased, but this change was only significant after midazolam administration (Table 3). Diazepam or midazolam administration was followed by a sustained and significant decrease in plasma norepinephrine at 5, 10, and 15 min (Figs. 1,2). In contrast, plasma epinephrine concentration was significantly below baseline only in group 2 (Figs. 1,2). The decrease in plasma norepinephrine levels that occurred with administration of both drugs correlated significantly with the values obtained in the awake state (Figs. 3,4). Systolic blood pressure was decreased significantly during each period of the study in both groups, whereas diastolic blood pressure decreased only in group 2 (Tables 1,2). Statistically significant but slight increases in Pa_{CO_2} and pHa were observed at 5, 10, and 15 min in the two groups, whereas Pa_{O_2} decreased only at 5 min in group 1 (Tables 1,2).

Discussion

The present study shows that administration of diazepam or midazolam resulted in a significant decrease in plasma norepinephrine concentration and in alteration of baroreflex control of heart rate. Plasma norepinephrine concentration represents only a small

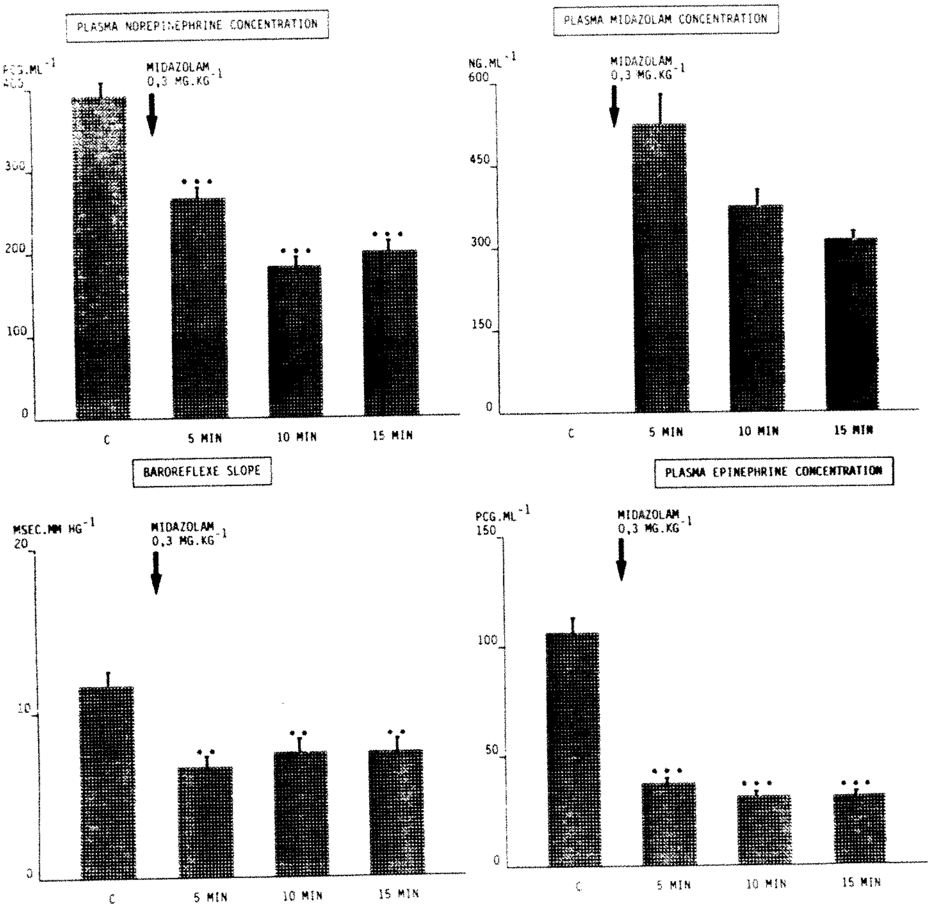

Figure 2. Baroreflex slope, plasma norepinephrine and epinephrine concentrations, and plasma midazolam concentration (mean ± SEM) plotted against time at each time of the study. Abbreviations: C, baseline period; others, see text; $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ vs C.

fraction of norepinephrine released from nerve endings after reuptake or metabolism. Thus small variations in such concentrations may reflect larger increases or decreases in norepinephrine release. However, plasma norepinephrine concentration is considered a reliable index of adrenergic activity (2) and, in addition, it responds rapidly to changing stimuli because of the short plasma half-life of norepinephrine (23). In contrast, plasma epinephrine concentrations represent mainly epinephrine released from the adrenal medulla. Depressed sympathetic activity has been observed with other anesthetic agents such as thiopental (3) and halothane after the first stages of inhalation anesthesia (24). Despite the absence of change in epinephrine levels in patients receiving diazepam, one can conclude from this study that diazepam and midazolam administration induced a sustained decrease in sympathetic activity.

We could not explain the absence of change in epinephrine concentration after diazepam administration, but a dissociation between epinephrine and norepinephrine changes was previously reported using thiopental (3). In our study, the decrease of plasma norepinephrine levels after diazepam or midazolam administration correlated significantly with the values measured in the awake state, indicating that depression of sympathetic activity was more marked in patients with a high adrenergic activity before drug injection. Similar findings were reported by Roizen et al. (2) during induction of anesthesia with a combination of either halothane or enflurane or morphine with thiopental. Thus it appears that reduction in sympathetic activity observed with most anesthetic agents except ketamine (25) is an univocal phenomenon related to the depression of central nervous system activity due to anesthesia. These changes could not be related to the moderate hemodynamic alterations or blood gas variations after the administration of diazepam or midazolam. Injection of phenylephrine could have induced a decrease of sympathetic activity by means of baroreflex response to an increase in blood pressure, but each blood sample for catecholamine determination was taken before each pressor test. At that time, blood pressure had always returned to preadministration levels. Thus the influence of phenylephrine injection on adrenergic activity could

Table 3. Pulse Interval at Reference Arterial Pressure (mean + SEM)

	n	Baseline	5 min	10 min	15 min
Group 1—diazepam R–R (msec)	9	718 + 35	888 ± 71	886 ± 91	957 ± 116
Group 2—midazolam R–R (msec)	9	715 ± 62	929 ± 90^a	1035 ± 118^c	996 ± 106^b

$^aP < 0.05$. $^bP < 0.01$. $^cP < 0.001$.

be eliminated. These results, i.e., decreased sympathetic activity after diazepam or midazolam, confirm previous hypotheses reported by Abel et al. (26) regarding the vasodilator effect of diazepam. The data obtained by Hoar et al. (17) concerning a combination of diazepam and morphine can also be explained by our findings regarding the action of diazepam on the sympathetic nervous system.

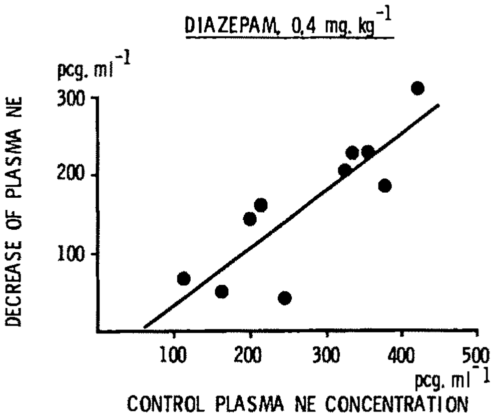

Figure 3. Plasma norepinephrine (NE) concentration while awake vs changes in plasma NE concentration after diazepam administration. A significant linear regression was found ($r = 0.852$; $P < 0.001$). Change = −40 + (plasma NE while awake) × 0.74.

The second main finding of this study is the alteration of baroreflex control of heart rate after diazepam and midazolam administration. These changes are related to plasma concentrations of diazepam and midazolam. The gain of the negative feedback mechanism by which the baroreceptors regulate the heart rate was thus decreased. Baroreflexes may be also affected by hypoxia or changes in Pa_{CO_2} (27). However, no hypoxemia was observed in our study. Moderate hypercarbia was present after administration of diazepam and midazolam, but Bristow et al. (27) showed that Pa_{CO_2} at 50 torr did not change baroreflex slope. The decrease of blood pressure induced by diazepam or midazolam may have resulted in a depression of calculated baroreflex gain by a shift to a flat portion of the relationship between arterial blood pressure and R–R interval. However, Smyth et al. (21), studying baroreflex changes during sleep, reported enhancement of baroreflex function, although the decrease in blood pressure during sleep in their study was similar to the decrease in blood pressure seen after diazepam or midazolam in the present study. Furthermore, Kotrly et al. (8) have shown that maintenance of blood pressure at awake values by continuous phenylephrine infusion does not change baroreflex gain. We have also observed a resetting of the baroreflexes: in the present study a lower arterial pressure was present with a heart rate not differing from the baseline level, although pulse interval at reference pressure increased significantly only after midazolam. Vagal mechanisms could also be involved in the maintenance of unchanged heart rates with a lower arterial pressure, but this component of the autonomic nervous system was not presently investigated. A decrease of baroreflex gain has been reported for other general anesthetics including thiopental (4), halothane, (5), enflurane (7), isoflurane (8), althesin (10), and a combination of morphine, N_2O, and diazepam (9). However, the effects of diazepam or midazolam on baroreflex control appeared less marked than those observed with halogenated anesthetics. The depression of baroreflex function with diazepam or midazolam is similar to that observed with intravenous anesthetics.

The site of action of anesthetics could be at one or several components of the baroreflex arc including baroreceptors, central nervous system, or effectors, as has been shown recently for halothane (12). Although the present study did not investigate the effect of diazepam and midazolam on the different components of the baroreflex, several hypotheses can be proposed. Regarding the effectors, a decrease in plasma norepinephrine concentration suggests a diminution of activity of the sympathetic efferent nerve pathway of the reflex. Moreover, a sustained decrease of sympathetic tone was observed, whereas the depression of baroreflex control of heart rate was more transient. Alteration of activity of vasomotor integrator centers that regulate cardiovascular reflex function is likely to

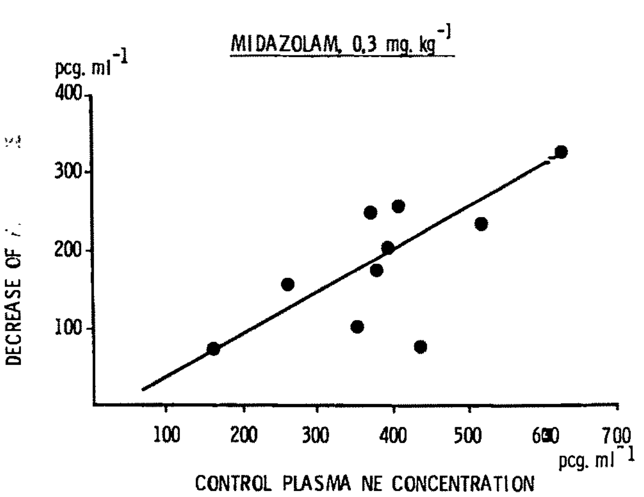

Figure 4. Plasma norepinephrine (NE) concentration while awake vs mean decrease in plasma NE concentration after midazolam administration. A significant linear regression was found (r = 0.760; $P < 0.02$). Change = −1 + (plasma NE while awake) × 0.52.

be involved with diazepam or midazolam, as has been reported to occur with diazepam in cats (19). Furthermore, a similar mechanism has been reported for barbiturates (4) and halogenated anesthetics (5,7,8). Regarding the effects of benzodiazepines on the baroreceptors, the observed decrease of adrenergic tone would have been expected to increase baroreceptor sensitivity (12,28).

The relation between the alteration of baroreflex control of heart rate and the reflex control of blood pressure remains speculative because the assessment of the heart rate response to an elevation of blood pressure does not provide information regarding the different functions of the baroreflex system. However, a comparison between several of the methods used to assess the different components of baroreflex function, i.e., pressor and depressor test, Valsalva maneuver, variable pressure neck chamber, has shown that there is a statistical positive relation between the results of these methods (29). Furthermore, recent studies with isoflurane (8) or morphine N_2O diazepam (9) have shown that the trend of the results obtained with the pressor test, the depressor test, or the neck suction test were similar. We conclude that both diazepam and midazolam produce alteration of baroreflex activity and a decrease of sympathetic tone. Although baroreflex depression associated with diazepam or midazolam is less marked than that produced by other general anesthetics, the use of diazepam or midazolam may be a potential hazard for induction of anesthesia in patients with acute hypovolemia. In contrast, the depression of adrenergic activity, after diazepam or midazolam administration, may be considered as advantageous in the clinical management of patients with coronary artery disease.

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The Pharmacokinetics and Maternal and Neonatal Effects of Epidural Lidocaine in Preeclampsia

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RAMANATHAN J, BOTTORFF M, JETER J, KHALIL M, SIBAI BM. The pharmacokinetics and maternal and neonatal effects of epidural lidocaine in preeclampsia. Anesth Analg 1986;65:120–6.

The pharmacokinetics and maternal and neonatal effects of epidural lidocaine were compared in ten preeclamptic and five normotensive women undergoing cesarean section at 36–40 weeks of gestation. Lumbar epidural anesthesia was achieved using 15–20 ml of 2% lidocaine without epinephrine. Serial venous samples for lidocaine levels were drawn from all the mothers during the procedure and up to 6 hr after the initial injection. Umbilical venous and arterial samples were drawn at delivery for measurement of neonatal acid–base status and lidocaine levels. There were no significant differences between normotensive and preeclamptic patients in the total dose of lidocaine, peak maternal plasma concentration, volume of distribution, maternal elimination half-life and umbilical vein/maternal vein ratios. The calculated area under the concentration time curve in preeclamptic patients (18.5 ± 4.7 $\mu g \cdot hr \cdot ml^{-1}$) was significantly greater than in normotensive mothers (14.1 ± 1.3 $\mu g \cdot hr \cdot ml^{-1}$) ($P < 0.02$). Total maternal body clearance in preeclamptic patients (24.5 ± 7.1 L/hr) was significantly lower than in normotensives (31.1 ± 4.4 L/hr) ($P < 0.05$). Neonatal outcome as evaluated by Apgar scores, umbilical arterial and venous blood gas tensions, umbilical vein/maternal vein ratios, and early neonatal neurobehavior scores at 4 hr and 24 hr after birth were similar in the two groups. The results indicate that the total maternal body clearance of lidocaine is prolonged in preeclampsia, and repeated administration of lidocaine can result in higher blood levels than in normotensive parturients.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL. ANESTHETICS, LOCAL—lidocaine. ANESTHESIA, OBSTETRIC. PHARMACOKINETICS—epidural lidocaine.

Lidocaine is a commonly used local anesthetic agent for regional anesthesia. Recent controversies regarding the cardiotoxic effects of bupivacaine and the neurotoxicity of 2-chloroprocaine have prompted a renewed interest in the use of lidocaine in obstetric patients (1,2). Studies have shown that lidocaine can be safely used for epidural anesthesia for vaginal deliveries and cesarean sections in normal pregnant patients (3,4). However, a detailed study of lidocaine in patients with severe preeclampsia is lacking. Therefore, we decided to study the pharmacokinetics and maternal and neonatal effects of lidocaine in patients with preeclampsia.

Methods

This study was approved by the Institutional Review Board, and informed consent was obtained from each patient. Fifteen patients undergoing cesarean section were studied. They were divided into two groups. Group I consisted of five normal healthy women with no obstetrical or medical complications. Group II consisted of ten patients with preeclampsia. Eight patients out of the ten in group II were diagnosed as having severe preeclampsia as evidenced by a systolic blood pressure of 160 torr or greater, or a diastolic pressure of 110 torr or greater on at least two occasions 6 hr apart; proteinuria of at least 5 g/24 hr (3+ or 4+); oliguria of 500 ml or less in 24 hr; cerebral or visual disturbances; epigastric pain and pulmonary edema; or cyanosis (5). All patients in group II were treated with a loading dose of magnesium sulfate ($MgSO_4$), 4–6 g, followed by 1–2 g/hr. In addition, two patients in group II also received hydralazine, 150 mg, in 150 ml of 5% dextrose in water as continuous intravenous infusions to decrease diastolic pressure below 110 torr.

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Patients in premature labor, patients with abnormal presentations, diabetes, preeclampsia superimposed on chronic hypertension, cardiac problems, respiratory diseases, hepatic or renal diseases, and those who were receiving chronic medications all were excluded from the study. None of the patients received any intravenous or intramuscular narcotics or sedatives within 2 hr before the beginning of the study. The laboratory data included complete blood count, hematocrit, serum electrolyte levels, coagulation studies, and liver function tests. Central venous pressure (CVP) was monitored in all preeclamptic patients and was maintained in the range of 6–8 cm H_2O by fluid administration.

All patients in both groups were in active labor prior to surgery. The indications for cesarean section in group I were previous cesarean section and cephalopelvic disproportion (CPD). In group II the indications for surgery were as follows: CPD, previous cesarean section, severe preeclampsia with inability to control blood pressure, and failure of labor to progress.

After we made sure that the coagulation studies were normal, epidural catheters were placed in the usual manner at the L3-4 interspace and 18–20 ml of 2% lidocaine without epinephrine was injected in divided doses. Anesthesia was achieved to the level T2-4 in all patients. Left lateral tilt was maintained, and oxygen was administered by face mask. Maternal blood pressure was measured every minute by an automatic blood pressure cuff. Maternal hypotension (in group II a 30% decrease in systolic pressure below preanesthetic level obtained after treatment with $MgSO_4$ and hydralazine and in group I a systolic pressure <100 torr) was corrected by increasing the rate of fluid administration and small doses of ephedrine. Samples of blood for lidocaine levels were drawn from a large indwelling venous catheter in the arm at 5, 10, 15, 20, 25, 30, 40, and 60 min and at 1.5, 2, 4, and 6 hr after completion of the injection of lidocaine. The samples were placed in ice, centrifuged, and frozen at −20°C until analysis. At the time of delivery, blood samples were drawn from umbilical artery and vein from doubly clamped sections of umbilical cords to measure blood gas tensions and lidocaine levels. The induction–delivery interval (ID interval) and the uterine incision–delivery intervals (UD interval) were recorded. The Apgar scores at 1 and 5 min were determined by pediatricians, and the early neonatal neurobehavior scores of Scanlon (ENNS) were performed at 4 hr and 24 hr of age. Sixty minutes after the initial injection, three patients in each group received an additional 120 mg of lidocaine, as they began to experience some discomfort. All patients received 2.5–5 mg of diazepam and 1–2 ml of fentanyl intravenously for sedation after the umbilical cord was clamped. No further sedatives or narcotics were given.

Plasma lidocaine levels were determined by fluorescent polarization immunoassay using the TDX drug analyzer system and assay kits from Abbott Laboratories. This immunoassay involves the competitive binding of the drug from the patient sample and a tracer-labelled analyte for antibody binding sites. A change in the polarization of the fluorescent light emitted by the tracer is measured by highly sensitive optic systems and is inversely related to the drug concentration (6). Compared with high pressure liquid chromatography (HPLC), the results indicate good correlation with a reported correlation coefficient of 0.944, a slope of 0.975, and an intercept of 0.096. This assay system has a sensitivity of 0.1 μg/ml and shows less than 0.5% cross reactivity with the metabolites monoethyl glycine xylidide (MEGX) and glycine xylidide (GX) (7).

For pharmacokinetic analysis, the following equations were used (8). The terminal elimination rate constant (β) was calculated by the terminal slope of the log-linear phase of the concentration–time curve. The elimination half-life was calculated by the equation

$$t_{1/2} = \ln (2)/\beta.$$

The area under the concentration–time curve (AUC) was calculated by the linear trapezoidal method by adding the AUC from 0–6 hr to the extrapolated value to infinity,

$$(\mathrm{conc}_{6H})/\beta$$

where conc_{6H} is the serum lidocaine concentration at 6 hr. Clearance (Cl) was calculated by the equation

$$\mathrm{Cl} = \mathrm{Dose}/2\mathrm{AUC}_{0-\infty}$$

and the apparent volume of distribution was calculated by

$$\mathrm{Vd}\beta = \mathrm{Dose}/\beta\text{-}\mathrm{AUC}_{0-\infty}.$$

The statistical analysis was performed using the Student's *t*-test and χ^2 analysis where appropriate, and a *P* value less than 0.05 was considered statistically significant. The data are presented as mean ± SD.

Results

The two groups of patients were similar in age, height, weight, and gestational age (Table 1). Mean arterial pressure (MAP) in group II (126.2 ± 7.19 torr) was significantly higher than in group I (83.8 ± 4.4 torr)

Table 1. Comparison of Patient Groups

	Group I (n = 5)[a]	Group II (n = 10)[a]
Maternal age (yr)	22.2 ± 2.49	20.6 ± 2.40
Maternal weight (kg)	73.3 ± 5.8	69.9 ± 5.7
Maternal height (cm)	64.0 ± 1.2	64.1 ± 1.9
Gestational age (weeks)	37.8 ± 1.5	37.9 ± 0.99
Infant weight (g)	3294 ± 209	3322 ± 404
Parity-primiparas (number)	2	8
Multiparas (number)	3	2

[a] Mean ± SD; no significant differences were noted.

Table 2. Intraoperative Data

	Group I (n = 5)[a]	Group II (n = 10)[a]
Mean maternal arterial pressure (torr)	83.8 ± 4.4	126.2 ± 7.19[b]
Time of onset of surgical anesthesia (min)	17.0 ± 2.8	16.8 ± 2.7
Amount of fluids administered (ml)	1120 ± 228	2016 ± 338[b]
Induction–delivery interval (min)	28.0 ± 4.5	27.3 ± 3.7
Uterine incision–delivery interval (sec)	88.0 ± 2.8	88.0 ± 4.2
Incidence of hypotension (number)	2	2

Statistical analysis by Student's t-test and χ^2 analysis.
[a] Mean ± SD.
[b] $P < 0.001$.

Table 3. Umbilical Venous and Arterial Blood Gas Data

	Group I (n = 5)[a]	Group II (n = 10)[a]
Umbilical Vein		
pH	7.35 ± 0.02	7.4 ± 0.02
Po_2 (torr)	32.0 ± 4.7	30.2 ± 1.6
Pco_2 (torr)	39.2 ± 2.3	38.0 ± 2.7
Base deficit (mEq/L)	−2.0 ± 1.7	−3.0 ± 2.1
Umbilical Artery		
pH	7.30 ± 0.02	7.30 ± 0.03
Po_2 (torr)	19.0 ± 1.8	18.0 ± 1.6
Pco_2 (torr)	49.0 ± 2.6	50.0 ± 2.0
Base deficit (mEq/L)	−5.0 ± 1.4	−3.7 ± 2.0

[a] Mean ± SD; no significant differences were noted.

(Table 2). The level of anesthesia (T2-4), the time of onset of surgical anesthesia, the incidence of hypotension, ID intervals, and UD intervals were similar in the two groups (Table 2). The amount of fluids administered in group II (2016 ± 338 ml) was significantly greater than in group I (1120 ± 228 ml) (Table 2).

Infant birthweights were similar in the two groups (Table 1). One baby in group II had an Apgar score of 4 at 1 min, but at 5 min, all babies in both groups scored above 7. The umbilical arterial and venous blood gas tensions and pH were normal in both groups of babies, and there were no significant differences between the two groups (Table 3). There were no significant differences between the groups for any of the variables tested in the ENNS at 4 and 24 hr (Table 4, Table 5). All babies were admitted to the normal newborn nursery, and none of the babies required special care.

Liver function tests were abnormal in six patients in group II in whom serum glutamic oxaloacetate transaminase levels were moderately elevated and alkaline phosphatase and lactic dehydrogenase levels were markedly elevated. Serum bilirubin was elevated in one of the six patients.

There were no significant differences between the two groups in the mean doses of lidocaine administered, peak plasma concentration, or the time to reach peak concentration (Table 6). At the time of delivery the mean maternal lidocaine plasma levels, umbilical venous lidocaine levels, and the umbilical vein/maternal vein lidocaine ratios were not significantly different in the two groups (Table 7). The AUC (Fig. 1, Table 8) was significantly higher in group II (18.5 ± 4.7 μg·hr·ml^{-1}) than in group I (14.1 ± 1.3 μg·hr·ml^{-1}). Similarly, total body clearance of lidocaine was significantly lower in group II (24.5 ± 7.1 L/hr) than in group I (31.1 ± 4.4 L/hr). The volume of distribution (Vd) and elimination half-life ($t_{1/2}\beta$) were not significantly different in the two groups (Table 8).

Discussion

The anesthetic management of patients with severe preeclampsia is controversial. Transient but severe hypertensive responses during endotracheal intubation under general anesthesia can lead to cerebral hemorrhage, pulmonary edema, and cardiac failure (9,10). Pretreatment with potent vasodilators may or may not attenuate such responses (9,10). The possible occurrence of laryngeal edema and the ever-present danger of maternal aspiration add to the dangers of general anesthesia.

When hypovolemia is corrected, and in the absence of coagulopathies, fetal distress, antepartum hemorrhage, and other absolute contraindications for major regional anesthesia, continuous lumbar epidural anesthesia is eminently suitable in patients with severe preeclampsia. In a recent study using the Xe^{133} clearance technique, Jouppila et al. showed that, in patients with severe preeclampsia, lumbar epidural anesthesia increased the intervillous blood flow by

Table 4. Percentage of Neonates with High Neurobehavioral Scores

		Group I (n = 5)[a]	Group II (n = 10)[a]
Pin prick	4 hr	60	50
	24 hr	100	90
Pull to sit	4 hr	40	40
	24 hr	80	70
Arm recoil	4 hr	40	40
	24 hr	80	50
Truncal tone	4 hr	20	50
	24 hr	60	40
General tone	4 hr	40	50
	24 hr	60	50
Rooting	4 hr	30	30
	24 hr	70	50
Sucking	4 hr	90	60
	24 hr	100	100
Moro	4 hr	60	50
	24 hr	60	60
Placing	4 hr	80	50
	24 hr	80	80
Alertness	4 hr	80	70
	24 hr	60	80
General assessment	4 hr	90	80
	24 hr	100	100
State	4 hr	60	70
	24 hr	80	70

No significant difference by χ^2 analysis was noted.
[a]All values are expressed as percentage.

Table 5. Percentage of Neonates with Response Decrements

		Group I (n = 5)[a]	Group II (n = 10)[a]
Pin prick decrement	4 hr	100	80
	24 hr	100	100
Sound decrement	4 hr	80	90
	24 hr	100	90
Light decrement	4 hr	80	80
	24 hr	100	90
Moro decrement	4 hr	80	70
	24 hr	100	90

No significant difference by χ^2 analysis was noted.
[a]All values are expressed as percentage.

Table 6. Lidocaine Dose and Peak Maternal Plasma Concentration

	Group I (n = 5)[a]	Group II (n = 10)[a]
Initial dose of lidocaine (mg)	370.0 ± 20.0	372.0 ± 27.0
Total dose of lidocaine (mg)	436.0 ± 50.0	422.0 ± 50.0
Peak plasma concentration (μg/ml)	2.8 ± 0.2	3.4 ± 0.8
Time to reach peak concentration (min)	34.0 ± 13.2	37.0 ± 13.0

[a]Mean ± SD; no significant differences were noted.

77% when the maternal mean arterial pressure was maintained at baseline levels (11).

Maternal Effects

The total dose of lidocaine administered to our patients is similar to that used in other studies (4,12). Epinephrine was not added to the local anesthetic solution in our study because preeclamptic patients are hypersensitive to vasopressors (9). In spite of the lower clearance of lidocaine in group II, none of the mothers experienced symptoms or signs of central nervous system toxicity. Hypotension in a normal pregnant patient is defined as 25–30% change of systolic pressure from baseline or a decrease in the systolic pressure below 100 torr. These criteria may not be acceptable in patients with severe preeclampsia with a higher baseline mean arterial pressure. We administered enough fluids to the preeclamptic patients to maintain the CVP at 6–8 cm H_2O. In spite of this, in two patients in this group the systolic pressure decreased below 100 torr but responded quickly to the administration of more fluids and small doses of ephedrine. The amount of fluids administered was significantly increased in our patients with severe preeclampsia, a finding already reported by Joyce et al. (13). No complications occurred in any of the mothers in the postpartum period. The liver function tests were normal in all patients at the time of discharge.

Neonatal Effects

In patients with severe preeclampsia there is a high incidence of growth retardation and premature labor (14,15). In our study, gestational age and birthweight in the two groups were similar. We did not include mothers with premature labor, abnormal presentations, and other complications such as diabetes mellitus and chronic hypertension, so that comparisons could be made between the groups. The Apgar scores, umbilical arterial and venous blood gases, umbilical vein/maternal vein ratio, and the ENNS were similar in the two groups of babies.

Lidocaine has a molecular weight of 234, and it easily crosses the placental barrier (16). The ratio between umbilical venous and maternal venous lidocaine levels at delivery was higher in the present patients than in previous studies (3,4,12), perhaps because we did not use epinephrine with the lidocaine; thus the result was that vascular absorption of lidocaine

Table 7. Maternal and Umbilical Venous Levels at Delivery and Umbilical Venous/Maternal Venous Ratios

	Group I (n = 5)[a]	Group II (n = 10)[a]
Maternal plasma level (μg/ml)	2.64 ± 0.2	3.15 ± 0.8
Umbilical vein level (μg/ml)	1.88 ± 0.36	1.71 ± 0.46
Umbilical vein/maternal vein ratio	0.71 ± 0.13	0.57 ± 0.18

[a] Mean ± SD; no significant differences were noted.

Table 8. Maternal Pharmacokinetic Data

	Group I (n = 5)[a]	Group II (n = 10)[a]	P
Area under the concentration–time curve (μg·hr·ml^{-1})	14.1 ± 1.3	18.5 ± 4.7	0.02[b]
Clearance (L/hr)	31.1 ± 4.4	24.5 ± 7.1	0.05[b]
Volume of distribution (Vd) (L)	154.1 ± 110.6	146.9 ± 45.7	NS
Elimination Half-Life ($t_{1/2}\beta$) (hr)	3.36 ± 2.2	4.47 ± 2.7	NS

[a] Mean ± SD.
[b] Statistically significant.
NS, Not significant.

after maternal injection was more rapid and thus maternal plasma levels and transfer of drug across the placental barrier were greater. In a recent study, Abboud et al. found that addition of epinephrine to lidocaine significantly lowers the placental transfer and the umbilical vein to maternal vein ratios (17). Even in normal pregnancy, asphyxia leads to acidosis and "ion trapping" of lidocaine in the fetus (16,18). To avoid further deterioration of the already compromised placental circulation in patients with severe toxemia, proper oxygenation of the mother and meticulous attention to avoiding factors leading to fetal asphyxia such as maternal hypotension and aortocaval compression are essential. The decreased placental perfusion in severe preeclampsia can also cause increased maternal lidocaine levels. In a recent study using the Brazelton Neonatal Neurobehavioral Assessment Scale (BNBAS), Kuhnert et al. found subtle changes in babies whose mothers received lidocaine for epidural anesthesia compared with those babies whose mothers received 2-chloroprocaine (19). The BNBAS was not performed in our study.

Pharmacokinetic Data

The pathophysiologic changes in preeclampsia such as decreased plasma volume, increased interstitial fluid volume, decreased plasma proteins, and decreased renal and hepatic function can all have profound influence on the maternal responses to drug therapy and drug disposition. The total dose of lidocaine administered in this study was 436 ± 50 mg in group I and 422 ± 50 mg in group II and the maternal level at delivery was 2.64 ± 0.2 μg/ml in group I and 3.16 ± 0.08 μg/ml in group II. These findings are comparable to levels reported by others (4,12). Shnider et al. found the ratio between maternal venous and maternal arterial levels for lidocaine with epinephrine was 76 ± 17.8 (20). In our study, serial arterial sampling might have shown a higher level with peak values occurring earlier because epinephrine was not added to the local anesthetic. The peak maternal levels (Table 6) in preeclamptic mothers shows a trend of higher levels than in normotensive mothers, but there were no statistically significant differences between the two groups. The calculated AUC (Fig. 1, Table 8) was significantly greater and the total body clearance significantly slower in the preeclamptic group than in normal parturients. There were wide individual variations in the Vd (Table 8) in both groups. Maternal elimination half-life ($t_{1/2}\beta$) was prolonged in both groups when compared with a half-life of 100-120 min for intravenously administered lidocaine in healthy volunteers (21). This is probably due to large Vd values and unpredictable vascular uptake from epidural lipid and protein depots when lidocaine is injected epidurally (16,21,22).

In a recent similar study, Kuhnert et al. (23) found that after lidocaine spinal anesthetic in healthy pregnant patients the drug is detectable in both maternal and neonatal plasma. The mean maternal lidocaine

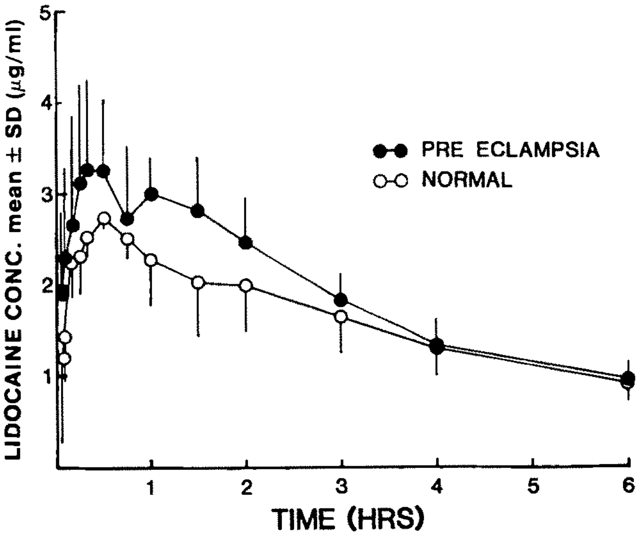

Figure 1. Mean lidocaine levels in group I and group II.

levels were lower than those found after epidural anesthesia. Spinal anesthesia is seldom used in patients with severe toxemia, as a precipitous fall in blood pressure is common due to the presence of hypovolemia in these patients (9).

Lidocaine is metabolized by hepatic microsomal enzymes, and clearance depends upon three factors: hepatic blood flow, hepatocellular function, and protein binding (24). First, lidocaine, with a high hepatic extraction ratio (0.63), has a clearance that is very sensitive to changes in hepatic blood flow (21,24). In severe preeclampsia, there is intense vasospasm involving all major vascular beds including the splanchnic vascular bed. This can decrease the hepatic blood flow. In addition, a previous study has shown that even in normal volunteers, epidural anesthesia with lidocaine without epinephrine decreased hepatic blood flow by 23% and the hepatic extraction ratio by 21%, while increasing splanchnic vascular resistance by 30% (25).

Second, in severe preeclampsia conventional liver function tests may be abnormal, and the more severe the preeclampsia the greater the degree of hepatic dysfunction (15,26,27). In addition, immunofluorescence studies on needle biopsies of liver in severe preeclamptic patients show generalized diffuse fibrin deposits in the hepatic sinusoids with focal ischemic necrosis of the hepatic parenchyma which also causes elevation of liver enzymes (28). In our study, six of the ten patients in group II had elevated plasma levels of liver enzymes.

Third, the unbound or free fraction of lidocaine in pregnant women is significantly greater than in nonpregnant women (29). Total plasma protein levels in patients with toxemia are decreased. However, a recent study has shown that the α-1 acid glycoprotein levels (a major binding site for lidocaine) are greater in preeclamptics than in normal parturients (30). The protein binding characteristics of lidocaine in patients with severe preeclampsia have yet to be studied. The etiology of decreased clearance of lidocaine in our group of severely preeclamptic mothers is therefore uncertain. We believe that a combination of all the above factors contributes to the decreased clearance of lidocaine.

In conclusion, the present results indicate that total body clearance of lidocaine is prolonged in preeclampsia, and this finding may become clinically significant with repeated injections of lidocaine because higher levels of the drug may be potentially neurotoxic.

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1986;65:127–32

Anesthesia for Hypoplastic Left Heart Syndrome:

Use of High-Dose Fentanyl in 30 Neonates

Dolly D. Hansen, MD, and Paul R. Hickey, MD

HANSEN DD, HICKEY PR. Anesthesia for hypoplastic left heart syndrome: use of high-dose fentanyl in 30 neonates. Anesth Analg 1986;65:127–32.

The anesthetic management of the first stage palliative surgical repair of hypoplastic left heart syndrome with a high-dose fentanyl (50 μg/kg)–pancuronium (0.14 mg/kg) anesthetic technique is described in 30 neonates. Previously this severe form of congenital heart disease carried a 100% rate of mortality. The pathophysiology that leads to this mortality is explained and related to the surgical procedure utilized for palliation. The major problem encountered intraoperatively was control of pulmonary blood flow. Management of the effect of anesthesia and intraoperative events on pulmonary blood flow was important because the rapid flux in pulmonary vascular resistance during the postnatal and perioperative period is the major destabilizing factor in these neonates. Ventricular fibrillation with surgical manipulation was a minor problem in the present series but was a major problem in an earlier series where a low dose narcotic–nitrous oxide technique was used. Ventricular fibrillation probably occurred due to the relative coronary insufficiency resulting from the anatomy present in this syndrome.

Key Words: ANESTHESIA, NEONATAL. HEART—hypoplastic left heart syndrome. ANESTHETICS, INTRAVENOUS—fentanyl.

Hypoplastic left heart syndrome (HLHS) is a complex of congenital anomalies of the aorta and the left side of the heart generally not associated with extracardiac congenital anomalies. Occurrence of HLHS has previously led to 100% mortality early in life despite numerous attempts at surgical palliation and correction (1–3). Advances in cardiac surgical techniques and growing understanding of single ventricle physiology have now made palliation and later Fontan type repair feasible without transplantation (4). Although HLHS occurs in 7.5% of infants with congenital heart disease, almost as frequent as isolated patent ductus arteriosus (5), anesthesiologists rarely have had occasion to care for these infants. Increasing numbers of neonates with HLHS are now presenting at infant cardiac centers for surgical repair. Anesthetic management of the neonate with HLHS has not previously been described in the literature.

The purpose of this report is to describe problems in the both anesthetic and perioperative management unique to newborns with HLHS and our experience with a high-dose fentanyl technique as one approach to these problems.

Physiology and Surgical Technique

In the typical HLHS syndrome, aortic valve atresia, hypoplasia of the ascending aorta, severe left ventricular hypoplasia, and hypoplasia of the mitral valve are combined (Fig. 1). Neonates with HLHS depend upon patency of the ductus arteriosus to provide systemic blood flow, but they may be asymptomatic until physiologic closure of the ductus arteriosus occurs. At that time, systemic and coronary perfusion becomes progressively insufficient, leading to metabolic acidosis, coronary ischemia, and eventually death.

In addition to ductal patency, the viability of HLHS infants is also dependent on a balanced level of pulmonary vascular resistance (PVR) relative to systemic vascular resistance (SVR) because both circulations are supplied from a single ventricle in a parallel fashion. The rapid decrease in the PVR that normally occurs early in neonatal life also takes place in neonates with HLHS, resulting in increasingly large pulmonary blood flow at the expense of systemic blood flow, a "pulmonary steal" phenomenon. In this situation, both coronary and systemic blood flow again become insufficient, leading to metabolic acidosis, high ouput cardiac failure, and death despite increasingly high levels of PaO_2 due to the large pulmonary flow.

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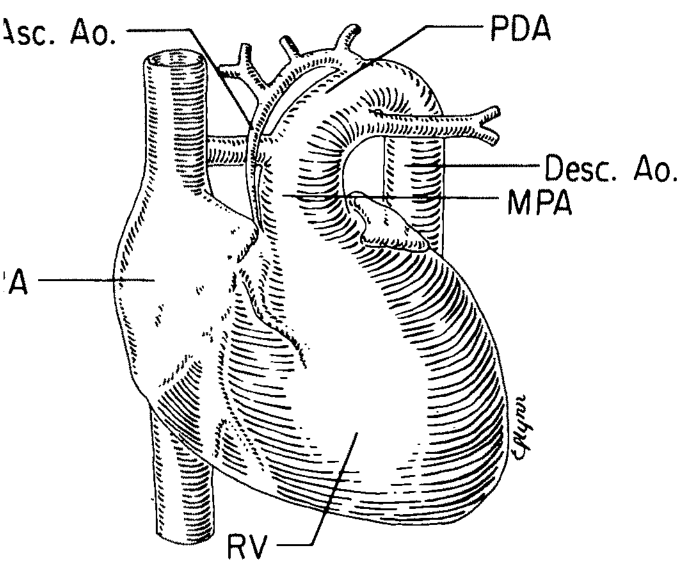

Figure 1. Anatomy of typical HLHS. Left ventricle is not seen because it is posterior and extremely small. Coronary flow is derived retrogradely down the hypoplastic arch. Abbreviations: Asc Ao, ascending aorta; PDA, persistent ductus arteriosus; Desc Ao, descending aorta; MPA, main pulmonary artery; RV, right ventricle; RA, right atrium.

Alternatively, any postnatal events that lead to elevation of PVR can easily reduce pulmonary blood flow to the point where arterial Po_2 becomes so low that progressive metabolic acidosis and finally circulatory failure result (Fig. 2). Because there is a rapid flux in PVR in the postnatal period, the necessary fine balance between PVR and SVR depicted in Figure 2 is unstable and difficult to maintain.

The completed palliative procedure shown in Figure 3 eliminates the need for a patent ductus arteriosus. The procedure is carried out by transsecting the pulmonary artery and using the proximal portion to reconstruct the ascending aorta. A systemic-to-pulmonary shunt to provide pulmonary flow is then connected from the reconstructed aorta to the oversewn stump of the distal pulmonary artery. This palliative procedure leaves the single (right) ventricle directly connected to the systemic circulation but also, via the shunt, connected to the pulmonary circulation in a parallel arrangement as before. The stage is then set for later correction with a Fontan-type procedure (anastomosis between the right atrium and pulmonary artery) when PVR has decreased to adult levels. The Fontan procedure, together with the elimination of the anatomic shunt, then separates the two circulations, thus resulting in normal arterial oxygen saturations.

Both before and after the palliative procedure, there is complete mixing of pulmonary venous and systemic venous blood in a single ventricle which is connected parallel to both the pulmonary and systemic circulations. The palliative procedure thus does not eliminate the need for the delicate balance shown in Figure 2 but does eliminate the need for ductal patency to provide adequate systemic flow, which is accomplished preoperatively by a prostaglandin E_1 infusion.

Patient Population and Anesthetic Management

We retrospectively reviewed the hospital courses of all HLHS neonates undergoing the Stage I palliative procedure at our institution during 1982 and 1983. Less severe variants of HLHS in which the prognosis is somewhat better were excluded. Descriptive statistics were compiled for three time periods: preoperatively in the intensive care unit before transport to the operating room, after induction of anesthesia before the start of cardiopulmonary bypass (CPB), and after the palliative procedure when the neonate had stabilized after CPB. We identified 30 neonates with typical HLHS who had been anesthetized with high-dose fentanyl technique, air-oxygen, and pancuronium for muscle relaxation. Only muscle relaxants and no anesthetics were used after CPB and subsequent deep hypothermic circulatory arrest because cerebral function typically is markedly depressed for several hours after the 45–60 min of circulatory arrest used for this procedure.

The infants were all neonates 6 ± 6 (SD) days old and 3.2 ± 0.4 kg in weight. Their mean hematocrit was 43 ± 8%, reflecting blood loss and transfusion during cardiac catheterization rather than degree of hypoxemia. Prostaglandin E_1 infusion for ductal patency was required preoperatively in 83%, inotropic support in 23%, and continuing bicarbonate infusions for acidemia ($pH < 7.30$) in 20%. The condition of the neonates generally had been stabilized as much as possible after their arrival at this hospital and subsequent cardiac catheterization. Usually umbilical artery and intravenous lines were in place prior to arrival in the operating room; infants receiving prostaglandin infusions had been intubated previously. After the routine monitoring of systemic arterial pressure, temperature, and ECG was begun, anesthesia was induced with between 50 and 75 μg/kg of fentanyl (mean 59 μg/kg) given simultaneously with 0.1–0.15 mg/kg of pancuronium (mean 0.14 mg/kg) over a period of 5–10 min during ventilation with 100% O_2. Neonates without endotracheal tubes were then intubated. Arterial blood gas tensions were measured after induction and a period of stable manual ventilation using an F_{IO_2} of 1.0. Time from incision to

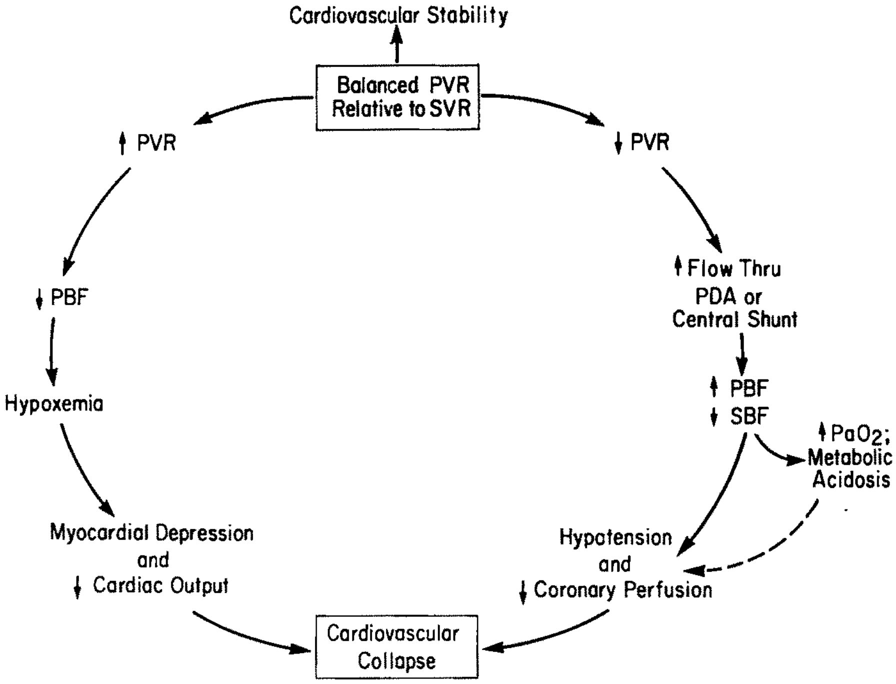
Cardiovascular Stability
Balanced PVR Relative to SVR
↑ PVR
↓ PBF
Hypoxemia
Myocardial Depression and ↓ Cardiac Output
↓ PVR
↑ Flow Thru PDA or Central Shunt
↑ PBF
↓ SBF
↑ PaO2; Metabolic Acidosis
Hypotension and ↓ Coronary Perfusion
Cardiovascular Collapse

Figure 2. Physiologic balance necessary for survival in HLHS before and after palliative surgical procedure. Before the palliation the connection between pulmonary and systemic circulations is provided by the ductus arteriosus. After the procedure the connection is provided by the central shunt. Abbreviations: PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; PBF, pulmonary blood flow; SBF, systemic blood flow; PDA, persistent ductus arteriosus.

beginning of cardiopulmonary bypass was rarely more than 20 min, during which time 10–15 ml/kg of crystalloid was infused.

If initial PaO_2 was greater than 100 mm Hg after induction, FI_{O_2} and ventilation were decreased, allowing $PaCO_2$ to increase and pH to decrease. These two maneuvers generally increase PVR and decrease pulmonary blood flow so that PaO_2 decreases. If necessary, positive end expiratory pressure (PEEP) was added to increase lung volumes also raising PVR and decreasing pulmonary flow, thus paradoxically lowering PaO_2 in the presence of HLHS with complete mixing of pulmonary and systemic venous return. These maneuvers were aimed at increasing systemic blood flow and pressure by reducing "pulmonary steal." In extreme cases of high pulmonary flow (judged by high PaO_2) and systemic hypotension, the surgeons were asked to put a temporary snare around the left or right pulmonary artery as soon as the heart was exposed to reduce pulmonary blood flow and thus raise systemic flow and pressure. The infants were placed on cardiopulmonary bypass (CPB) and cooled to <20° C, after which the circulation was arrested for 40–60 min while the aortic arch was reconstructed. The last part of the surgical procedure was the creation of a systemic-to-pulmonary shunt after CPB had been reinstituted and the infant was being rewarmed. After completion of the reconstructive procedure, weaning from CPB was accomplished with or without inotropic support.Dopamine or isuproterenol was used generally when inotropic support was necessary, depending on the PVR.

The most frequent problem encountered after bypass was too little pulmonary blood flow with resultant arterial hypoxemia ($PaO_2 < 20$ mm Hg). This was treated with hyperventilation to an alkalotic pH and a low $PaCO_2$ (20–25 mm Hg) (6,7), elevation of systemic arterial pressure, a trial of isoproterenol infusion to decrease PVR, and partial CPB support to increase PaO_2 and myocardial oxygenation for a short period of time. When pulmonary blood flow was inadequate as judged by the PaO_2 (direct measurement of pulmonary flow being technically infeasible), the pattern of ventilation seemed to be almost as important as minute volume of ventilation in increasing pulmonary blood flow. With persistent use of the measures outlined above, the arterial oxygenation usually improved to viable levels (PaO_2 30–40 mm Hg) as length of time after termination of CPB increased.

A less common problem was too much pulmonary blood flow after bypass, indicated by levels of $PaO_2 > 50$ mm Hg. In this event, manipulations similar to those used after induction when an excessively high PaO_2 occurred were again used to decrease pulmonary blood flow. As previously described, these maneuvers included decreases in FI_{O_2} and ventilation, along with application of PEEP if necessary. If a $PaO_2 > 50$ mm Hg was allowed to persist in the operating room or intensive care unit postoperatively, a progressive metabolic acidosis developed because of inadequate

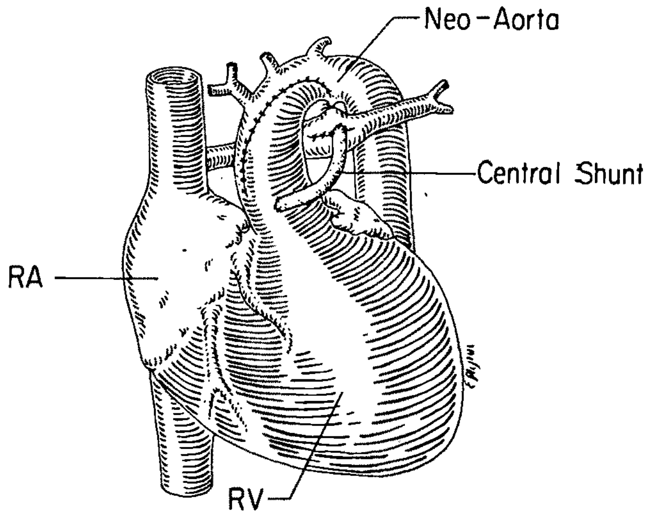

Figure 3. Anatomy after first stage palliative procedure for HLHS in the neonatal period. Ascending aorta has been reconstructed from the proximal pulmonary artery. Abbreviations: RA, right atrium; RV, right ventricle (single ventricle).

systemic flow. If the manipulations described above could not control the high pulmonary blood flow, the size of the systemic-to-pulmonary shunt had to be reduced.

Results and Outcome

Table 1 shows the vital signs, arterial blood gas tensions, and requirements for inotropic support and prostaglandin E_1 infusion at comparable times in each infant before operation in the ICU and after induction of anesthesia. Vital signs, requirements for support, and arterial blood gas tensions were similar before and after anesthesia was induced except for the markedly higher PaO_2 and a mild respiratory alkalosis after induction of anesthesia. One neonate (3.3%) developed ventricular fibrillation (VF) during initial surgical manipulation of the heart; defibrillation was readily accomplished using countershock with return of adequate systemic pressure.

Table 2 shows the clinical status of 29 infants when stable in the operating room after CPB and their requirements for inotropic support compared to inotropic support needed before bypass. The level of PaO_2 and its low variability are noteworthy. One neonate who had been in severe, intractable congestive heart failure prior to operation failed to regain cardiac function after CPB.

Fresh whole blood was given after bypass to maintain ventricular filling pressures at levels adequate to assure an appropriate systemic perfusion pressure. Bleeding from the extensive aortic and pulmonary arterial suture lines, together with the coagulopathy associated with CPB, plus extensive dilution of the neonate's blood volume by the pump prime often necessitated the transfusion of several blood volumes in the immediate postbypass period. Adequacy of intravascular volume replacement was determined by intra- and postoperative measurement of atrial pressures using intracardiac catheters (a large atrial septal defect is created intraoperatively if not previously present, essentially making the left and right atrium into a common chamber). Fresh blood, frozen plasma, and platelets were used liberally intraoperatively when clotting was felt to be inadequate and postoperatively after specific clotting studies were obtained. The accompanying large citrate loads in a neonate necessitated large quantities of calcium to support ionized calcium levels after CPB. Frequent measurement of ionized calcium levels was required to guide calcium therapy in this period.

Table 1. Clinical Status Before and After Induction of Anesthesia (Mean ± SD)

Variable	Before anesthesia (ICU)	After induction (OR)
Systemic systolic blood pressure (mm Hg)	69 ± 7	68 ± 10
Heart rate (beats/min)	149 ± 8	143 ± 13
Systemic arterial pH	7.39 ± 0.09	7.52 ± 0.09
PaO_2 (mm Hg)	50 ± 13	159 ± 120
$PaCO_2$ (mm Hg)	35 ± 7	29 ± 7
Inotropic support (%)	23	23
Prostaglandin E_1 infusion (%)	83	83

In the intensive care unit inotropic and ventilatory support was continued as described for the period after CPB. The infants were sedated with 0.1 mg/kg morphine, but later in the series they were sedated with infusions of fentanyl given together with pancuronium to facilitate control of ventilation until hemodynamic stability was attained. Time of ventilatory support varied from 3 days to several weeks, the median time being 7 days. The surviving infants were discharged 16 days to more than 2 months postoperatively; the median discharge time was 30 days.

Of 30 infants, 14 were discharged from the hospital (47%), 1 died in the operating room (3%), 6 died in the intensive care unit within 24 hr (20%), and there were 9 late hospital deaths (30%) for an overall mortality rate of 53%.

Observations and Discussion

The results reported above demonstrate that the high-dose fentanyl-pancuronium technique used in the

Table 2. Clinical Status Before and After CPB (Mean ± SD)

Variable	Before bypass (n = 30)	After bypass (n = 29)
Systemic systolic blood pressure (mm Hg)	68 ± 10	68 ± 8
Heart rate (beats/min)	143 ± 13	141 ± 12
Systemic arterial pH	7.52 ± 0.09	7.47 ± 0.09
Pa_{O_2} (mm Hg)	159 ± 120	31 ± 8
Pa_{CO_2} (mm Hg)	29 ± 7	41 ± 12
Inotropic support (%)	23	70

present series provides good cardiovascular stability in infants with HLHS. We surveyed 10 cases operated upon during our early experience with HLHS in 1980–81 when morphine (0.3 mg/kg)–metubine (0.4 mg/kg) –nitrous oxide was the anesthetic technique used. These 10 cases were quite similar to the cases in the present series, but a high incidence (50%) of VF was noted during initial surgical manipulation prior to bypass in the earlier group, compared to 3% in the present group. This earlier group was not concurrent with the present series. Subsequent changes in surgical technique, preoperative preparation, and anesthetic management prevent strict comparison of the incidence of VF with the two different anesthetic techniques.

A probable cause of the low threshold for VF in HLHS before palliation is insufficient coronary blood flow. Because the upper half of the body receives arterial blood flowing retrograde up the arch from the ductus arteriosus, the coronary bed is perfused by blood flowing in a retrograde direction through a long, hypoplastic ascending aorta. This anatomic situation results in a pathophysiology somewhat analogous to left main coronary artery stenosis in an adult and is corrected during the palliative operation. For presumably similar reasons, a high incidence of intraoperative VF also is seen in neonates with critical aortic stenosis prior to valvotomy.

Although it would be speculative and unjustified to attribute the low incidence of VF in the present series (3%) solely to use of the high-dose fentanyl–pancuronium technique, this potential problem of VF should be noted and guarded against. The danger of VF together with the often borderline cardiac status of the HLHS neonate argues against the use of potent inhalational agents such as halothane in these patients. Neither further lowering of the threshold for ventricular arrhythmias with halothane nor the potent negative inotropic effect of halothane in immature hearts (8) would seem advisable in these neonates. In contrast, large doses of fentanyl, together with pancuronium, have been shown to provide hemodynamic stability in infants (9).

The major clinical change in neonates with HLHS after induction of anesthesia with the present technique was the increase in Pa_{O_2} and its large variability indicated by the high standard deviation. Regardless of the FI_{O_2}, a high Pa_{O_2} in the presence of HLHS with complete mixing of pulmonary and systemic venous blood implies a very high pulmonary blood flow at the expense of the systemic circulation. In the majority of our patients this was not reflected by a lower systolic arterial pressure after induction, presumably because alterations in peripheral vascular tone temporarily compensated for the decreased systemic flow which would be accompanied by a progressive metabolic acidosis. We usually did not see a metabolic acidosis prior to cardiopulmonary bypass in these patients because the period of low systemic flow was brief. In neonates who had persistently elevated levels of Pa_{O_2} (>100 mm Hg) after induction of anesthesia and were unresponsive to the maneuvers described above, temporary ligation of one pulmonary artery prior to bypass would typically increase systemic arterial pressure by 20–30 mm Hg and would decrease Pa_{O_2} back to preoperative levels (approximately 40–50 mm Hg).

When Pa_{O_2} increased appreciably above 50 mm Hg for more than a brief period pre- or postoperatively in either the intensive care unit or the operating room, the progressive metabolic acidosis described above would develop if pulmonary blood flow was not decreased by appropriate maneuvers. In turn, the progressive metabolic acidosis led to further decreases in systemic output and eventual cardiovascular collapse, accounting for a large part of the early postoperative mortality.

The reason for the large increase in Pa_{O_2} (and presumably the large increase in pulmonary flow) with the induction of anesthesia is unclear. Neither reduction of oxygen consumption with paralysis and anesthesia nor decreases in intrapulmonary shunting (at cardiac catheterization pulmonary venous blood was usually highly saturated with oxygen indicating little intrapulmonary shunt) are likely to be a large factor. Use of 100% O_2 during induction usually leads to a decrease in PVR in normal neonates, increasing pulmonary flow and perhaps accounting for some of the rise in Pa_{O_2} observed in our patients. In addition to the use of 100% O_2, the hyperventilation after induction, shown by the increase in pH and decrease in Pa_{CO_2} after induction (Table 1), probably also contributed to the decrease in PVR and the increase in pulmonary blood flow (6,7).

Large increases in pulmonary blood flow occur at the expense of systemic flow, so use of 100% O_2 for induction might be criticized. However, as seen from the large variability in the PaO_2 measured after induction of anesthesia, some infants do not increase their PaO_2 with induction so that initial use of a low FI_{O_2} might be hazardous and lead to irreversibly low levels of PaO_2 and cardiovascular collapse. In those infants in whom PaO_2 increases substantially after induction, pulmonary blood flow can be controlled using the maneuvers described above.

Balancing pulmonary and systemic flow as depicted in Figure 2 is problematic during induction of anesthesia and subsequent surgical manipulations, but PVR and SVR can be highly variable after CPB, increasing the problem. Because of increases in PVR with CPB and circulatory arrest, the high reactivity of the neonatal pulmonary circulation, and infusion of large amounts of blood products, the PVR tends to be high at the time of termination of CPB. In this situation, achieving the necessary fine balance between pulmonary and systemic flows in a univentricular, parallel circulation is a real challenge. Although neonatal hearts tolerate low arterial saturations in the absence of acidemia, low pulmonary blood flows after CPB resulting in levels of $PaO_2 < 20$ mm Hg and arterial oxygen saturation of <50% were not tolerated despite good systemic flow and pressure.

Although size of the surgically created shunt is a potentially limiting factor in determining pulmonary flow, flow through prosthetic shunts is passive rather than autoregulated by smooth muscle activity in vessel walls. The prosthetic shunts used were not restrictive enough to prevent alterations in pulmonary blood flow, and thus alterations in arterial oxygenation, whenever relative pulmonary and systemic vascular resistance changed. The impact of various anesthetic manipulations, anesthetic agents, surgical interventions, and ventilation on this fragile balance is poorly understood. The effects of amount and pattern of ventilation, lung volumes, FI_{O_2}, pH, and anesthetic agents on pulmonary vascular resistance are poorly understood in neonates and require further study. The techniques described above that we have used to compensate for fluxes in PVR and systemic vascular resistance in neonates with HLHS are largely empirical. The present technique using high doses of fentanyl may be of benefit in stabilizing the pulmonary circulation in these infants because high doses of fentanyl have been shown to blunt stress responses in the pulmonary circulation of infants (10). However, there are few other data available to suggest appropriate management techniques.

Surgical techniques for management of HLHS are still evolving, as is our understanding of the anesthetic techniques useful in managing the problems outlined above. The incidence of the perioperative anesthetic problems in the present series is, however, lower than in our previous series of patients with HLHS, partly through more aggressive use of the management techniques outlined above and partly through improvements in surgical technique. With this evolution, the hospital discharge rate after the initial palliative procedure in this once uniformly fatal form of congenital heart disease is now above 50% in several centers. At our institution, for example, hospital mortality for this procedure in all admitted neonates with HLHS was 24% (6 of 25) during the most recent period from January 1984 to July 1985 for a hospital discharge rate of 76%. Further improvements in anesthetic and surgical techniques for HLHS as well as future investigation into the control of PVR hopefully will continue to improve survival in this population of otherwise normal babies.

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Cardiac Dysrhythmias Induced by Infusion of Local Anesthetics into the Lateral Cerebral Ventricle of Cats

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HEAVNER JE. Cardiac dysrhythmias induced by infusion of local anesthetics into the lateral cerebral ventricle of cats. Anesth Analg 1986;65:133–8.

The hypothesis that neurogenically mediated cardiac arrhythmias can be induced by the intracerebroventrical (ICV) infusion of local anesthetic solutions was tested in 11 chronically prepared, unmedicated cats. Test substances were bupivacaine (0.1%), lidocaine (0.4%), procaine (0.4 or 0.8%), or saline (pH 5.8). Cats received one or more of the test substances with two or more days between infusions. Four cats were also given bupivacaine intravenously at 1.1 and 1.4 mg/kg to help determine whether ECG changes after ICV injection of local anesthetic were due to direct cardiac action after systemic absorption. Total dose was 3.8–7.8 × the largest ICV dose (0.7 mg). No ventricular arrhythmias were observed after the ICV infusion of saline or with intravenous doses of bupivacaine as large as 1.4 mg/kg. Only one of six cats given lidocaine ICV developed sustained, severe ventricular arrhythmias. Five of seven cats given ICV procaine developed ventricular arrhythmias. All ten cats given ICV bupivacaine developed ventricular arrhythmias. It is concluded that local anesthetics can produce neurogenically mediated ventricular arrhythmias in cats and that, of the three local anesthetics tested, bupivacaine is the most potent and effective and lidocaine is the least potent and effective.

Key Words: ANESTHETICS, LOCAL—bupivacaine, lidocaine, procaine. HEART, ARRHYTHMIAS—local anesthetics. TOXICITY—local anesthetics.

The report by Albright (1) of six incidents of cardiovascular collapse from rapid injection of local anesthetics stimulated considerable interest in the relative cardiovascular toxicity of this group of drugs. There is some evidence that bupivacaine and perhaps some other local anesthetics have unique cardiotoxic activity. For instance, de Jong et al. (2) reported that subconvulsant doses of bupivacaine and etidocaine can precipitate cardiac arrhythmias in cats, whereas lidocaine does not.

Investigations aimed at identifying the mechanism of the cardiotoxicity have focused on the direct effects of local anesthetics on the heart (3–5). It is possible, however, that part of the cardiotoxic effects of local anesthetics are neurogenically mediated (i.e., alter neural control of heart rate or rhythm). Many drugs are known to have profound cardiovascular effects that are mediated by a neurogenic mechanism. Most notable are cardiac glycosides that can produce ventricular arrhythmias via a central nervous system action (6).

In the study reported here, the hypothesis that local anesthetics can produce neurogenically mediated ventricular arrhythmias was tested by infusing bupivacaine, lidocaine, procaine, and vehicle into the lateral cerebral ventricle of chronically prepared cats while arterial blood pressure, ECG, and EEG were monitored.

Methods

The *NIH Guide for the Care and Use of Laboratory Animals* was followed. Stainless steel cannulas (Harvard Apparatus, Newport Beach, CA) were placed into the right lateral cerebral ventricle of 11 healthy cats (anterior 11.5 mm, lateral 3.0 mm, and ventral 7 mm (7)). Electrodes fashioned from stainless steel sewing machine needles were also implanted into the skull of five cats for EEG recording and a cannula (PE90 tubing) in a femoral artery for blood pressure recording. The electrodes were soldered to a connector, and the connector and ventricular cannula were affixed to the skull with dental acrylic. The arterial cannula was tunneled under the skin and externalized at the back of the neck. Heparinized saline (1 USP unit/ml) was locked in the cannula by heat sealing the externalized end of the cannula. The animals were anesthetized with halothane for the surgical preparation then given

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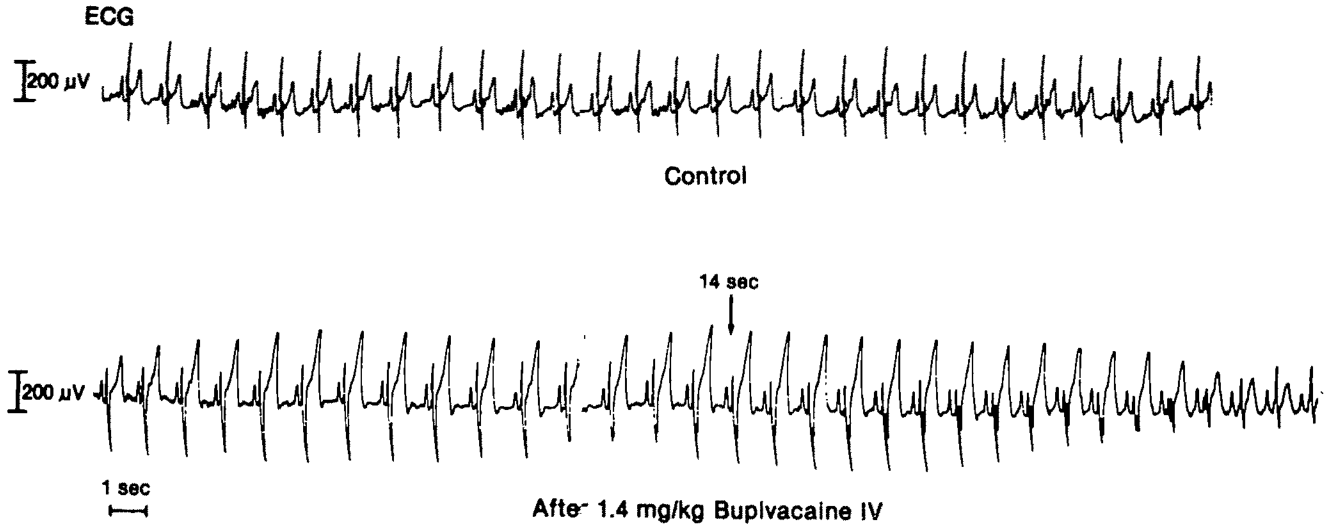

Figure 1. ECG before and after injection of bupivacaine 1.4 mg/kg intravenously. Nature and duration of ECG changes are shown on bottom trace.

a week or more to recover from surgery before drug infusions were begun.

Preparatory to intracerebroventricular (ICV) infusion of test substances, cats were placed in canvas bags and needle electrodes were placed subdermally in the right forelimb and left hindlimb for recording lead II ECG. The arterial cannula was prepared for blood pressure recording by placing a Luer connector on the externalized end, which was then connected to a blood pressure transducer. A mating plug was attached to the connector fixed to the skull for EEG recording. The cap and stylus of the intracerebroventricular cannula were removed, and needle stock that fit snugly into the cannula was inserted through the cannula into the ventricle. Polyethylene tubing calibrated at 100 µl volumes and containing 350 µl test substance was attached to the needle stock.

ECG was recorded on a polygraph in all cases, and when technically feasible, EEG and arterial blood were also recorded (e.g., arterial line patent). After control recordings were obtained from the unmedicated cats, a test substance was administered via gravity flow from the PE tubing. Flow was controlled by a clamp on the end of the tubing and by raising or lowering the tubing; no air was allowed to enter the ventricle. Average infusion time was 22 sec. Test substances were bupivacaine HCl (0.1%), lidocaine HCl (0.4%), procaine HCl (0.4 or 0.8%), or saline (pH 5.8). Local anesthetic solution was prepared by dissolving crystalline salt in 0.9% NaCl solution. The mixture was then passed through a microbial filter into a sterile container. Aseptic technique was used for the ICV infusions. If arrhythmias were not produced by the initial infusion, repeat infusions were made at 5-min intervals until arrhythmias developed or until cumulative dose was judged to be excessive. At the beginning of the study, four cats were only given bupivacaine as an initial test of the hypothesis. Positive results stimulated expansion of the study to compare the ability of various local anesthetics to produce neurogenically mediated cardiac arrhythmias. Animals were allowed to recover two or more days between infusions.

Bupivacaine was infused in 100 µg or 300 µg increments at 5-min intervals. Procaine was infused in 400 µg or 800 µg increments. Lidocaine was infused in 400 µg or 800 µg increments. Saline was infused in 100 µl or 300 µl increments. Appearance of CSF in the cannula hub when the stylus was removed and free-flow of test substance through the cannula were taken as evidence the infusions were made into the lateral ventricle.

Four cats were also given bupivacaine intravenously to help determine whether ECG changes after ICV injection of local anesthetics were due to direct cardiac action after systemic absorption. A rapid intravenous bolus of 1.1 mg/kg and 1.4 mg/kg was given with doses administered 4 days apart. Only ECG was recorded. Total dose of bupivacaine was from 2.64 mg to 5.46 mg. ECGs were evaluated for arrhythmias. Sinus tachycardia was not considered to be an arrhythmia.

Results

Intravenous Bupivacaine

None of the four cats given 1.1 mg/kg or 1.4 mg/kg bupivacaine intravenously had grand mal seizures,

Table 1. Heart Rate Changes (beats/min)[a]

Cat	Saline	Lidocaine	Procaine	Bupivacaine	Bupivacaine intravenously 1.1 mg/kg	Bupivacaine intravenously 1.4 mg/kg
A	35	130	200	135		
B	45	110	130	145		
C	80	30	20			
D	35	20	50	35		
E		60	70	130	−15	−5
F	60		90	25	5	5
G	20	50	40	65	−10	−10
H				130		
I				115		
J				110		
K				135	−30	[b]
Mean (± SD)	46(21)	67(44)	86(62)	102(44)[c]	−12(14)	−3(8)

[a] Heart rate after drug subtracted from control rate.

[b] Could not be determined.

[c] Significantly different ($P < 0.005$) from saline and intravenous bupivacaine values.

and only brief ECG disturbances were observed. Within 1–3 sec after the injections were finished, the T wave became elevated, QR amplitude decreased, and RS amplitude increased (Fig. 1), except in one case after 1.4 mg/kg where all components of the ECG became markedly smaller. These ECG changes lasted from 4 sec to 36 sec. Average heart rate change after 1.1 mg/kg and 1.4 mg/kg bupivacaine injection was −12 and −3 beats/min, respectively (Table 1).

ICV Saline

None of the six cats given ICV infusions of up to 900 μl saline developed cardiac arrhythmias, nor were any noteworthy changes in EEG activity observed in the four instances in which EEG was monitored (Table 2). Elevation in heart rate was seen in every animal after saline infusion. Average change was 46 beats/min (Table 1). Systolic blood pressure also rose from a baseline mean of 157 mm Hg (range 110–250) to an average maximum of 230 mm Hg (range 150–380) after saline infusion.

ICV Lidocaine

Only one of the six cats given lidocaine ICV developed sustained, severe ventricular arrhythmias (Table 2). Cumulative doses of up to 9.6 mg were given. Heart rate of all cats increased. Average change was 67 beats/min (Table 1). Substantial increases in systolic blood pressure were noted in the two cats whose blood pressure was recorded; in one case it increased from baseline level of 150 mm Hg to a maximal level of 320 mm Hg. In the other case, it rose from 260 mm Hg to 400 mm Hg. The latter case involved the animal who developed AV block. The other cat did not develop an arrhythmia (Fig. 2).

ICV Procaine

Five of seven cats given ICV procaine developed ventricular arrhythmias (Table 2). Cumulative doses required to produce these arrhythmias ranged from 1.2–9.6 mg. None of the cats exhibited seizure activity, and in four cases EEG recording revealed no preseizure or seizure activity.

Heart rate in all animals increased after procaine infusion. Average change was 86 beats/min (Table 1). Systolic blood pressure rose from 190 mm Hg to 320 mm Hg (no arrhythmias) in one animal and from 270 mm Hg to 450 mm Hg in another animal (1 PVC).

ICV Bupivacaine

Six cats were given 100 μg bupivacaine infusions at 5-min intervals (Table 2). All developed ventricular arrhythmias including PVCs, bigeminy, quadrigeminy, and ventricular tachycardia. Cumulative doses required to produce these arrhythmias were 200–700 μg. Blood pressure was recorded in one of these cats; it rose from a baseline of 205 mm Hg systolic to greater than 270 mm Hg systolic after bupivacaine infusion. EEG in this cat revealed no seizure or preseizure activity, nor were behavioral signs of seizure activity observed in the other five cats.

All four cats given a single ICV infusion of 300 μg bupivacaine developed ventricular arrhythmias, including PCVs and ventricular tachycardia which lasted from 1 min 39 sec to 12 min 45 sec (Table 2; Figure 3). Time to onset of arrhythmia ranged from 20 sec

Table 2. Duration of Arrhythmias

Cat	Drug (dose in μg)			
	Bupivacaine	Procaine	Lidocaine	Saline
A	12 min 45 sec (300)	14 min (2400)	2 PVCs (2400)	— (300)
B	1 min 39 sec (300)	— (2400)	— (1200)	— (300 × 3)
C	NT	3 min 32 sec (800 × 2)	— (400 × 4)	— (100 × 9)
D	3 min (100 × 3)	1 PVC (800 × 3)	AV block after (400 × 9)	— (100 × 6)
E	37 sec (100 × 2)	— (800 × 8)	— (400 × 5)	NT
F	4 min (100 × 7)[a]	2 PVCs (400 × 3)	NT	— (100 × 8)
G	16 sec (100 × 2)[b]	— (800 × 9)[c]	2 min 24 sec (400 × 7)	— (100 × 8)
H	5 min 10 sec (300)	NT	NT	NT
I	9 min 40 sec (300)	NT	NT	NT
J	2 min 4 sec (100 × 6)	NT	NT	NT
K	7 min (100 × 7)	NT	NT	NT

Abbreviations: NT, not tested.

[a] Stopped after 10 mg/kg pentobarbital intramuscularly.

[b] 1 min 23 sec after third × 100.

[c] After 800 × 9, 2400 PVC, Bigeminy, V Tach.

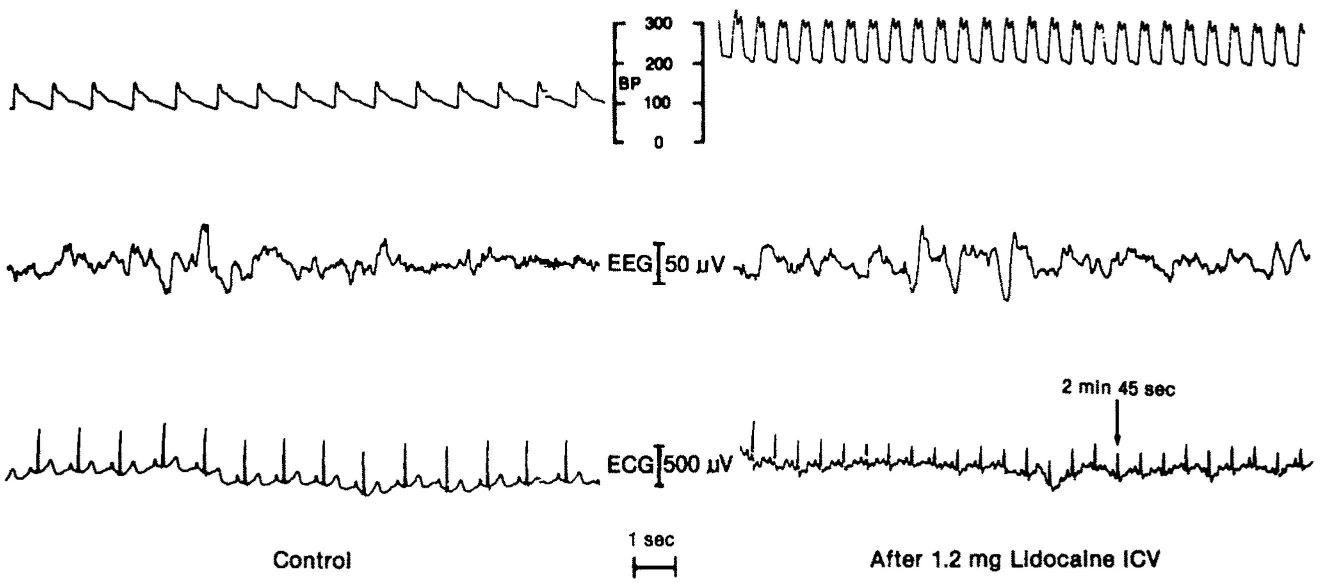

Figure 2. EEG, ECG, and blood pressure (BP) recording before and after ICV infusion of 1.2 mg lidocaine. Note the marked increase in heart rate and blood pressure but absence of ventricular arrhythmias.

to 2 min 23 sec after infusion was completed. None of the cats exhibited behavioral or EEG signs of seizure activity.

Heart rate increased in all cats given ICV bupivacaine. Average increase was 102 beats/min. This change was significantly different ($P < 0.05$; Student's t-test) from the changes after intravenous bupivacaine and ICV saline. Systolic blood pressure rose from an average baseline value of 146 mm Hg (range 105–190) to a maximum of 294 mm Hg (range 235–330) after bupivacaine infusion. Signs of respiratory embarrassment were not observed after infusion of any of the drugs.

Discussion

These results show that bupivacaine, procaine, and lidocaine can produce ventricular arrhythmias when infused into the lateral cerebral ventricle of cats. Bupivacaine appears to be the most potent agent for this effect and lidocaine the least potent. Ventricular arrhythmias were consistently produced by bupivacaine, whereas lidocaine produced sustained ventricular arrhythmias in only one cat. Animal-to-animal variation in dose of any one local anesthetic required to produce arrhythmias is probably due to a host of factors, including variability of cannula tip location

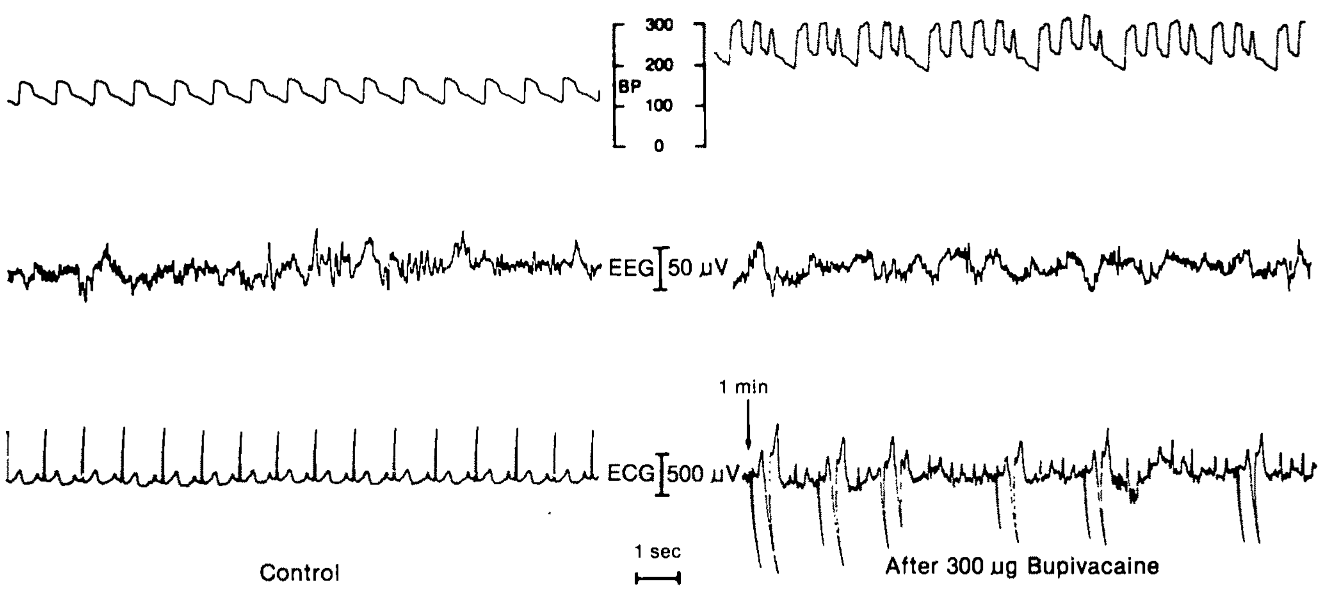

Figure 3. EEG, ECG, and BP recording before and after ICV infusion of 300 μg bupivacaine. Note premature ventricular contractions with no corresponding pulse pressure, and elevated blood pressure.

relative to the neural structure(s) that mediate the effect.

Where ICV-infused local anesthetics act and how they act to produce ventricular arrhythmias are not known, nor are the distribution parameters of ICV infused local anesthetics defined. However, results of this study support the conclusion that the arrhythmias are not due to direct effect of local anesthetic on the heart because direct intravenous injection of bupivacaine doses substantially greater than injected ICV produced benign and very transient ECG changes. Considering that approximately equipotent nerve conduction block doses served as the starting point for this study (8), the differences in arrhythmogenicity indicate that the local anesthetic action of the agents may not cause the arrhythmias.

Perhaps there is similarity between the CNS effects of local anesthetics and cardiac glycosides. Digitalis-induced arrhythmias have been associated with increased norepinephrine turnover in the brain (9). Central α_2 receptor mediation of the cardiotoxic actions of digoxin has been proposed (10). Plunkett and Tackett (10) suggested that central Na^+–K^+ ATPase inhibition by the cardiac glycosides may trigger neurotransmitter release in the CNS resulting in α_2 receptor activation.

Han and Moe (11) demonstrated that excitation of the sympathetic nerves to the heart in dogs can increase dispersion and nonuniformity of the ventricular refractory period and predispose the heart to ventricular fibrillation. Direct electrical stimulation of the ventromedial hypothalamus, the reticular formation, or central gray substance of the midbrain results in sympathetically mediated elevation of blood pressure and arrhythmias (12).

In humans and dogs, lidocaine (1–2 mg/kg intravenously) increases arterial pressure (13). The increase is due to increased contractile force of the heart or to an increased cardiac output via a lidocaine action on the brain. Both sympathetic and vagal pathways are involved. Chinn et al. (14) demonstrated that ICV injection of 300–1000 μg lidocaine in urethane-immobilized rats produced variable responses including pure pressor, pure depressor, and biphasic responses. These findings, coupled with my observations, indicate possible different mechanisms for the hypertensive action of ICV-administered local anesthetics and the arrhythmogenic action. However, there apparently is a positive correlation between the ability of ICV-infused local anesthetics to increase heart rate and to cause ventricular arrhythmias. It is possible that the rapid heart rate limits coronary perfusion thereby producing hypoxia induced arrhythmias.

Nontoxic doses of bupivacaine (2 mg/min for 3 hr) have been shown to produce similar cardiovascular changes in humans as does 1–2 mg/kg lidocaine (15). The investigators concluded, however, that the effects are probably caused mainly by a direct effect of bupivacaine on the cardiovascular system, because only quantitatively minor changes in plasma catecholamines and other endocrine metabolic parameters were observed. These findings, however, do not rule out the possibility of autonomic nervous system involvement in the arrhythmogenic (cardiotoxic) effects of local anesthetics.

In summary, results of this study show that ICV-administered local anesthetics can produce cardiac arrhythmias in cats via a neurogenic mechanism. Potency and efficacy for the effect varied among the drugs tested; bupivacaine was the most potent and effective and lidocaine was the least potent and effective. Further study is needed to determine what role, if any, this property of local anesthetics plays in toxic cardiovascular responses to these drugs observed clinically.

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Lidocaine Disposition in Mother, Fetus, and Neonate after Spinal Anesthesia

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Although it is generally believed that concentrations of local anesthetic in maternal plasma do not reach levels that affect the fetus after spinal anesthesia, there are few studies that have measured drug levels in either maternal or neonatal plasma after spinal anesthesia. The purpose of this study was to document the disposition of lidocaine in mother, fetus, and neonate after spinal anesthesia using gas chromatographic/mass spectrometric measurement of lidocaine and two metabolites of lidocaine. Plasma concentration time curves, fetal/maternal ratios, cord artery/cord vein ratios, and neonatal urine levels were determined in ten patients. The results document that lidocaine is present in maternal and neonatal plasma. Mean (± SD) maternal plasma levels (0.65 ± 0.52 µg/ml) were significantly lower than those previously reported after epidural anesthesia (2.09 ± 1.31 µg/ml). Fetal/maternal plasma concentration ratios averaged 0.37 ± 0.2 and mean cord arterial/cord venous ratios 0.5 ± 6.7. Lidocaine and its metabolites were present in neonatal urine for longer than 36 hr. This study demonstrates that spinal anesthesia with lidocaine results in neonatal exposure to lidocaine.

Key Words: ANESTHETIC TECHNIQUES—spinal. ANESTHESIA—obstetric. ANESTHETICS, LOCAL—lidocaine.

According to US national statistics (1,2), spinal anesthesia remains the preferred regional anesthetic technique for cesarean section. Because small quantities of local anesthetics are used for spinal anesthesia and the rates of drug absorption from the subarachnoid space are slow, it has been assumed that maternal blood levels are low or nondetectable (2). Furthermore, low maternal levels would mean that little of the local anesthetic agent would cross the placenta and reach the fetus (2). However, these concepts are theoretical because maternal, fetal, or neonatal levels of local anesthetics after spinal anesthesia have not been published widely.

Even though spinal anesthesia has been used for over 85 years, it was not until 1979 that Giasi et al. measured blood levels of local anesthetics after spinal anesthesia (3). The authors found, in nonpregnant subjects, that peak plasma levels of lidocaine after injection into the lumbar subarachnoid space were no different than when an equal amount of lidocaine was injected into the lumbar epidural space. Although blood levels were achieved more rapidly with epidural than with spinal anesthesia, there was no statistically significant difference in the maximum plasma concentrations achieved. Giasi's work has been repeated recently in other nonpregnant subjects with similar findings (4,5). These reports suggested that similar findings would be observed in obstetric patients and that placental transfer would occur after spinal anesthesia, especially because lidocaine as well as its two active metabolites are known to reach the infant (7). In 1980, Datta et al. reported detectable levels of lidocaine in both maternal and fetal plasma at delivery after subarachnoid injection (6).

The purpose of this study was to document the disposition of lidocaine and two of its metabolites in maternal, fetal, and neonatal plasma and neonatal urine after spinal anesthesia for delivery and to compare these data with those previously obtained from

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Table 1. Characteristics of the Maternal Study Population

Maternal characteristics	Mean ± SD	Range
Age (yr)	22.7 ± 3.4	19–29
Parity		
Nulliparous	0	
Multiparous	10	
Delivery Method		
Primary cesarean	2[a]	
Repeat cesarean	8	
Intrapartum anesthesia		
Total mg lidocaine in 7.5% dextrose	78.5 ± 12.3	50–100
Anesthesia–delivery interval (min)	6.6 ± 0.8	15–18
Complications		
Weight < 100 lb	1	
Weight > 200 lb	1	
Heavy smoking	2	

[a] One breech, one midpelvis distortion secondary to auto accident.

this laboratory (7) after epidural anesthesia had been given.

Materials and Methods

Subject Population and Administration of Anesthesia

Ten pregnant women and their infants were studied after delivery by elective cesarean section. To qualify, the patients had to be classified as ASA categories I or II. The clinical characteristics of the mothers and neonates and the amount of drug and timing of anesthesia are shown in Tables 1 and 2. This study was approved by the Human Investigation Committee of Cleveland Metropolitan General Hospital, and informed consent was obtained from each patient before inclusion in the study.

Preoperatively, the patients were given prophylactic antacids (oral Mylanta 30 ml) and hydrated with 1000–2000 ml lactated Ringer's solution or normal saline. Subcutaneous injection of 2-chloroprocaine (1–2 ml of 1%) was used to numb the skin prior to dural puncture. Sixty to 100 mg of 5% lidocaine with 7.5% dextrose was then injected into the subarachnoid space after dural puncture with a 25-gauge needle at the L2–3 or L3–4 interspace and the patients immediately placed in the supine position with left lateral displacement of the uterus. This provided a level of anesthesia to approximately T4. Only one patient was given lidocaine with epinephrine (0.2 ml, 1:1000). All patients received supplemental oxygen via nasal cannula. All of the women underwent scheduled cesarean sections at what was considered to be term, although three infants were found to be 36 weeks of gestational age by Dubowitz examination (8). All infants were delivered within 15–18 min after induction of spinal anesthesia. One infant had a 1-min Apgar score of four, which was the only low Apgar score in the study. This infant had a cord vein pH of 7.32. At delivery, two infants (both 36 weeks) had cord vein pH values less than 7.25. However, both had Apgar scores of 7 or better at 1 min. In all three cases, the mothers had had hypotension corrected with ephedrine prior to delivery. There were no differences in the fetal:maternal plasma concentration ratios of lidocaine in these three infants. All infants were healthy and were discharged from the hospital with their mothers.

Table 2. Characteristics of the Neonatal Study Population

Neonatal characteristics	Mean ± SD	Range
Number of infants	10	
Gestational age (weeks)	39.9 ± 2.3	36–42
Birthweight	3135 ± 388	2360–3650
Apgar score < 7		
1 min	1	
5 min	0	
Cord venous pH	7.305 ± 0.06	7.195–7.410
Cord arterial pH	7.264 ± 0.07	7.113–7.384
Complications		
< 37 weeks gestation	3	
Large for gestational age	1	

Sample Collection

Maternal peripheral venous blood samples (3 ml) were collected from an indwelling cannula in the arm opposite to that with intravenous infusion before and 1, 3, 5, 7, 10, 15, and 20 min after subarachnoid injection or until delivery and then every 30 min until 2–3 hr had elapsed since injection. A maternal venous sample was also obtained coincident with clamping of the infant's cord. All samples were drawn into heparinized tubes and immediately placed on ice. The plasma was removed after centrifugation and frozen until assayed by gas chromatography/mass spectrometry (GC-MS). Neonatal blood samples obtained at birth from a doubly clamped section of umbilical cord and again 24 and 48 hr after delivery by either heel stick or venipuncture were obtained and handled in the same manner as maternal blood samples.

Six consecutive 6-hr samples of neonatal urine were collected after delivery in plastic urine collection bags (Hollister Newborn U-bag). Neonatal urine collections were stopped if signs of skin irritation occurred. All urine samples were frozen until analyzed.

Sample Analysis

Lidocaine and the two pharmacologically active metabolites produced by successive dealkylation—monoethylglycinexylidide (MEGX) and glycinexylidide (GX) were determined in plasma and urine using the method of Hignite et al. (9) with a Hewlett-Packard 5995A quadrupole table-top mass spectrometer interfaced to the gas chromatograph with a glass jet separator (7). A 1.3 m × 2 mm inner diameter AW DMCS treated glass column packed with 3% OV-1-OV-17 (6:1) coated on an 80–100 mesh Supelcoport (Supelco, Bellefonte, PA) was used. The instrument conditions include a carrier gas flow rate of 20 ml/min, an injection port temperature of 250°C and an oven temperature programmed from 176°C (0 min) at 14°C/min to 220°C (0.5 min); and the entire run time was 3.6 min. The mass spectrometer was autotuned at mass/charge ratio (m/z) 100. Standard curves were prepared and the samples quantitated using the Hewlett–Packard software for automatic quantitation of selected ion monitoring data by area normalization on m/z 86 (for lidocaine), m/z 100 (for MEGX), and m/z 114 (for GX and the internal standard, W-12174) (7).

Pharmacokinetic Analysis

Semilogarithmic plots of levels of lidocaine and its metabolites in maternal plasma were obtained by plotting concentrations of drugs in maternal plasma against minutes after the injection of lidocaine. Fetal: maternal plasma concentration ratios were calculated by dividing the amount of lidocaine and metabolites in cord venous plasma at birth by the amount in maternal venous plasma at birth. The ratios between cord arterial and cord venous lidocaine concentration were obtained by dividing the concentrations at delivery in the cord arterial blood by those found in the cord venous blood. Linear plots showing urinary levels of lidocaine and two active metabolites, MEGX and GX, as a function of time were also constructed. Urinary levels of drug or metabolite data were expressed as μg/ml urine.

Statistical Analysis

Student's *t*-tests were used to compare levels of lidocaine in maternal venous, cord venous, and cord arterial plasma after spinal or epidural anesthesia. Significance was accepted at $P < 0.05$.

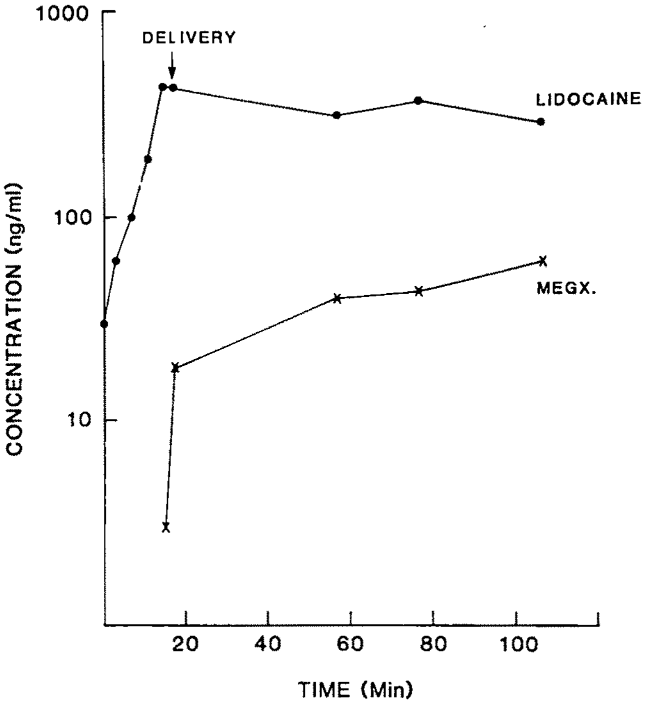

Figure 1. Maternal plasma lidocaine and MEGX levels after spinal anesthesia for delivery.

Results

Lidocaine and Metabolite Levels in Maternal Plasma

Figure 1 is a representative plasma concentration–time profile of lidocaine and MEGX after spinal anesthesia; GX was not detectable. Seventy-five mg of lidocaine was administered to this parturient. Lidocaine was detectable in plasma immediately thereafter and slowly increased in amount until a peak level was reached 16 min after administration that was maintained for several hours after delivery. In this case, the metabolite MEGX was detectable within 15 min and then increased rapidly, followed by a slow but steady increase for several hours. In four of the mothers, MEGX was not detectable in plasma until after delivery. GX was rarely detectable in any maternal plasma samples during the study period.

Mean levels of lidocaine in maternal plasma at delivery are shown in Table 3, along with the ranges of values. All but three of the levels were between 0.422 and 0.780 μg/ml. One patient who received only 60 mg of lidocaine and the one patient who was given lidocaine with epinephrine had lower levels of 0.101 and 0.267 μg/ml, respectively. One patient, who received 100 mg of lidocaine, had a plasma lidocaine level at delivery of 2.02 μg/ml.

Maternal levels of MEGX at delivery ranged from

Table 3. Lidocaine Concentrations in Maternal and Fetal Plasma at Delivery (µg/ml)

	Lidocaine	
	Mean ± SD	Range
Maternal venous plasma	0.65 ± 0.52	0.10–2.02
Fetal plasma		
Cord vein	0.20 ± 0.12	0.09–0.48
Cord artery	0.08 ± 0.06	0.00–0.22
Cord artery/cord vein	0.50 ± 0.27	0.04–0.96
Cord vein/maternal vein	0.37 ± 0.19	0.10–0.84

Table 4. MEGX Concentrations in Maternal and Fetal Plasma at Delivery (ng/ml)

	MEGX	
	Mean ± SD	Range
Maternal plasma	11 ± 14	0–32
Fetal plasma		
Cord vein	18 ± 2	0–72
Cord artery	17 ± 3	0–86
Cord artery/cord vein[a]	2.2 ± 2.4	0.24–6.5
Cord vein/maternal vein[a]	5.7 ± 5.9	0.6–14.4

[a] $n = 6$.

0 to 0.32 µg/ml with a mean of 0.011 ± 0.014 µg/ml. Both lidocaine and MEGX were usually detectable in maternal plasma for at least 24 hr. GX was not detectable until after delivery and only trace levels were apparent thereafter.

Fetal and Neonatal Plasma Levels

At delivery all cord venous and arterial samples had detectable lidocaine concentrations. Mean levels and range of values are shown in Table 3. Cord artery/cord vein ratios as high as 0.96 were found. After delivery, 50% of the neonates had detectable plasma levels of lidocaine and/or MEGX for 48 hr or longer; two infants had detectable plasma levels of GX.

At delivery, all cord venous samples had detectable MEGX concentrations, but not all of the cord arterial samples did. Mean MEGX levels and range of values are shown in Table 4. In those cases where MEGX was detectable in both cord arterial and venous blood, the cord arterial/venous ratio was usually greater than one. Furthermore, the cord venous/maternal venous ratio was usually greater than one. GX was not detectable in fetal plasma at delivery.

Neonatal Urine Levels

Twenty-eight urine samples were collected from nine infants. No complete 36-hr collections were obtained. Data from the urine samples that were obtained indicate that lidocaine, MEGX, and GX are detectable in neonatal urine for at least 36 hr after spinal anesthesia (Fig. 2). The amount of lidocaine excreted in urine decreased rapidly 12 hr after delivery, whereas the levels of MEGX increased during the first 12 hr and were sustained during the 36-hr collection period. Very low levels of GX were noted initially; these doubled after 18 hr of life. Levels of all three compounds at 36 hr of age suggested that excretion would continue for at least 72 hr.

Discussion

The purpose of this study was to describe the disposition of lidocaine in mother, fetus, and neonate after lidocaine spinal anesthesia for cesarean section. The key finding is that lidocaine rapidly crosses the placenta and reaches the fetus. This transplacental passage occurs despite injection of only small doses of lidocaine into the subarachnoid space and short drug-to-delivery intervals.

We are aware of only one other study of lidocaine levels after spinal anesthesia in obstetric patients or neonates with which to compare this study (6). Therefore, comparisons are also made with studies of nonpregnant subjects (3) and obstetric patients after epidural anesthesia (7).

Datta et al. first reported lidocaine levels in maternal and cord venous plasma at delivery (6). The mean levels of lidocaine reported by Datta et al. in maternal venous plasma, cord venous plasma, and cord arterial plasma (0.63, 0.17, and 0.11 µg/ml, respectively) are almost identical to those in the present study. Furthermore, the previous study reported a fetal/maternal plasma concentration of 0.40, whereas in the present study the value was 0.37. The agreement between the two studies is excellent. However, the earlier study is incomplete because Datta et al. confined their study to samples obtained only at delivery. They did not quantitate lidocaine metabolites and they did not determine drug levels in neonatal urine.

Several of the findings of this study are comparable to those in nonpregnant subjects published recently by Giasi et al. (3). They found peak levels of lidocaine at 15 min after injection into the subarachnoid space. In the present study, the peaks occurred 16–18 min after injection. The shape of the plasma concentration–time profiles in the study of Giasi et al. is also very similar to ours. However, there are also differences between the two studies. For example, Giasi et al. did not quantitate MEGX or monitor plasma levels of lidocaine beyond 30 min. Furthermore, mean peak

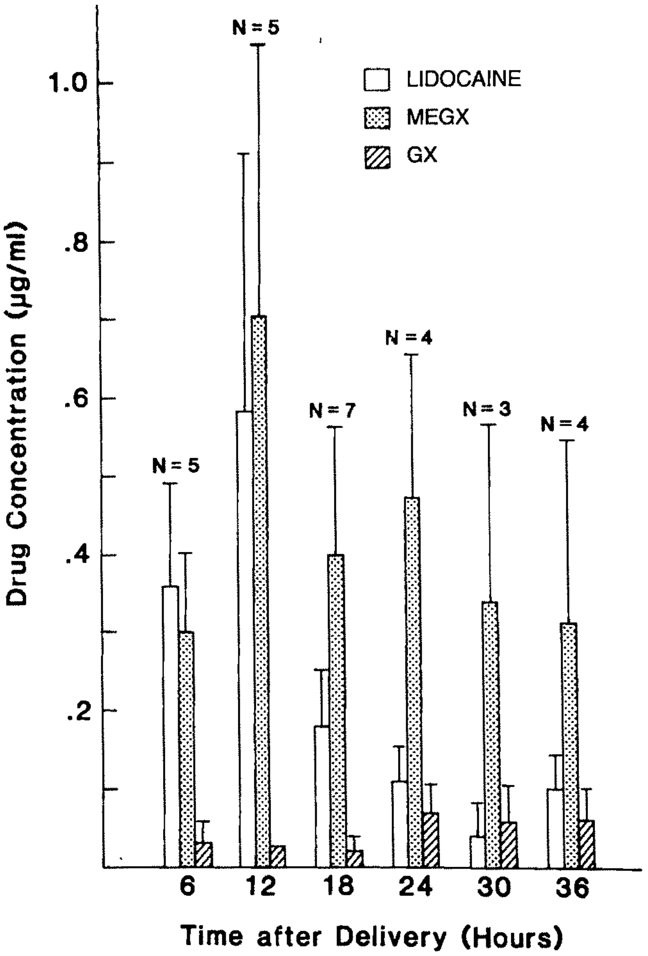

Figure 2. Neonatal excretion of lidocaine, MEGX and GX for 36 hr (mean ± SEM).

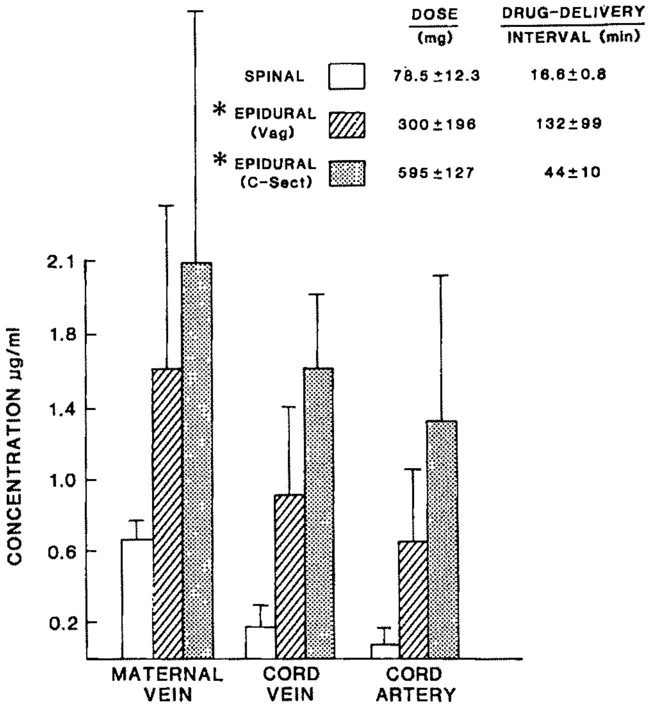

Figure 3. Comparison of plasma lidocaine levels at delivery after spinal or epidural anesthesia. The asterisk refers to previous study results (7).

lidocaine levels reported by Giasi et al. of 0.32 ± 0.07 µg/ml are lower, but within the range of the 0.64 ± 0.52 µg/ml found in the present study. This may be due to the differences in analytical techniques used to measure lidocaine or to the fact that our patients were pregnant. Vascular absorption of local anesthetics injected into the subarachnoid space is thought to occur from the subarachnoid space, the epidural space, and the spinal cord itself (10). During pregnancy, increased intraabdominal pressure causes venous engorgement, particularly in the epidural space (2). This results in decreased epidural space volume and possible decreased volume of cerebral spinal fluid in the subarachnoid space. These changes could account for the increased plasma levels that were noted in the present study and by Datta et al. (6).

It is known that lidocaine as well as its two metabolites reach the infant after epidural anesthesia and that lidocaine appears in maternal plasma within 1 min (7). The primary metabolite of lidocaine, MEGX, appears within 10 min and its secondary metabolite, GX, within 45 min. Fetal/maternal venous concentration ratios are 0.66, 1.45, and 1.03, respectively, for lidocaine MEGX and GX after cesarean section performed under epidural lidocaine anesthesia. Postpartum, the infant excretes all three compounds for at least 72 hr. On a mg drug/µg creatinine basis, the infant excretes more lidocaine and lidocaine metabolites than does the mother. The present study is the first to provide comparable data for disposition of lidocaine after spinal anesthesia.

In the present study, mean maternal lidocaine levels were one-third those found after the higher doses of lidocaine used for epidural anesthesia (7). Figure 3 compares the dosages and levels of lidocaine found after spinal anesthesia in the present study with those reported previously after epidural anesthesia had been administered (7). This difference is statistically significant at $P < 0.05$. Mean cord venous levels of lidocaine are one-quarter or one-eighth those found after epidural anesthesia for vaginal delivery or cesarean section, respectively, and cord arterial levels are also much lower (7). These comparisons are also shown on Figure 3, and the differences are statistically significant at $P < 0.05$. Mean plasma MEGX levels at delivery (not shown) were one-tenth those found previously after epidural anesthesia for cesarean section

(7). This is probably due to the shorter time interval between administration of the parent drug and delivery in the present study. The excretion pattern of lidocaine and MEGX was similar to what has been reported previously after epidural anesthesia had been administered (7).

It has been the general impression that concentrations of local anesthetics in maternal plasma never reach a level that could possibly affect the fetus after spinal anesthesia (2). In general, however, mean plasma levels are much lower than those reported previously after epidural anesthesia had been given (7), but individual mothers may have plasma levels comparable to those seen after epidural anesthesia for cesarean section despite the lower doses and shorter drug-to-delivery intervals with spinal anesthesia. Blood levels are also achieved more slowly after spinal anesthesia.

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1986;65:145–50

A Comparison of the Effects of Alfentanil Applied to the Spinal Cord and Intravenous Alfentanil on Noxiously Evoked Activity of Dorsal Horn Neurons in the Cat Spinal Cord

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MATSUMOTO M, COLLINS JG, KITAHATA LM, YUGE O, TANAKA A. A comparison of the effects of alfentanil applied to the spinal cord and intravenous alfentanil on noxiously evoked activity of dorsal horn neurons in the cat spinal cord. Anesth Analg 1986;65:145–50.

The purpose of this study was to examine the effects of alfentanil applied to the surface of the spinal cord and the effects of intravenously administered alfentanil on noxiously evoked activity of dorsal horn neurons. Extracellular single neuron recordings were obtained from wide dynamic range neurons in 26 decerebrate cats with transected spinal cords. Spinally administered alfentanil, 25 μg or 50 μg, caused 36 and 86% suppression of noxiously evoked activity, respectively. Maximum mean suppression was achieved at 24 and 21 min after 25 μg and 50 μg, respectively. Intravenous naloxone, 0.1 mg, when tested, completely reversed the suppression. Spontaneous recovery to control values occurred within 2 hr. Intravenously administered alfentanil, 12.5 μg/kg or 25 μg/kg, produced suppression of 43 and 89%, respectively, with maximum mean suppression observed at the 6- and 3-min time points, respectively. Complete recovery after intravenous administration was seen within 30 min. This study, using a sensitive neurophysiologic assay, demonstrates the important differences in onset and duration of drug effects that must be considered when comparing the responses of spinal cord neurons to intravenously administered narcotics and narcotics applied directly to the surface of the spinal cord.

Key Words: ANALGESICS—alfentanil. SPINAL CORD—effects of narcotics.

The development of intrathecal or epidural opiate administration provided the clinician with another important pain relieving technique. More importantly, it greatly enhanced our awareness of the importance of spinal cord pharmacology. As our understanding of spinal cord pharmacology increases, the great differences in the timing of drug action produced when drugs are administered near the spinal cord become apparent. As pointed out in a recent review of the intrathecal and epidural administration of opioids (1), the time course associated with those routes of administration is very different from that seen after systemic drug administration. This should be especially true for a drug like alfentanil that is unique among opiates of potential usefulness for intrathecal or epidural administration because of its kinetics after systemic administration (2). Alfentanil has a relatively small volume of distribution; combined with its clearance, this accounts for its short duration of action after systemic administration. These characteristics, as well as alfentanil's lipid solubility and potency that are greater than morphine, may be desirable in certain situations where spinal opioid analgesia is needed. This study was conducted in order to demonstrate, using a sensitive neurophysiologic assay, the great difference in onset and duration of action seen when alfentanil is placed at the spinal cord rather than administered intravenously. Spinal administration, as used in this study, involved the direct placement of drug onto the surface of the spinal cord (dura mater opened, pia mater and arachnoid intact) in the region from which electrical activity was being recorded. This technique approximates drug placement after spinal intrathecal administration.

Methods

All relevant institutional, state, and federal guidelines concerning the use of laboratory animals in research

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were followed in this study. Twenty-six cats of either sex weighing 2.5–4.5 kg were prepared for electrophysiologic experiments. Under halothane, nitrous oxide, and oxygen anesthesia, a tracheostomy was performed. The animals were artificially ventilated after paralysis with gallamine administered via an external jugular vein catheter. One of the carotid arteries was catheterized to permit monitoring of arterial blood pressure. The animals were rendered decerebrate by electrolytic lesions in the midbrain reticular formation, and anesthesia was discontinued. The spinal cord was transected at T-12 in order to remove supraspinal effects on the neurons under study. A laminectomy was performed from the L-4 through the L-6 spinous processes, exposing the lumbar spinal cord. The dura mater was incised and reflected and the spinal cord was bathed in 37°C physiologic saline. Blood pressure, body temperature, and end-tidal P_{CO_2} were monitored and maintained within normal limits.

After surgical preparation and a minimum of 2 hr after the end of anesthesia, a tungsten microelectrode was advanced into the dorsal horn of the spinal cord in order to obtain extracellular recordings of electrical activity from single wide dynamic range (WDR) neurons. Identification of neuron type was based upon the depth of the microelectrode and characteristic responses of the cell to the following stimuli: air puff, light touch with a camel hair brush, pinch with forceps, noxious radiant heat. A typical WDR neuron would demonstrate increased firing frequency to increasing intensity of stimulation with maximum response to a noxious stimulus.

After isolation and characterization of a single WDR neuron, control noxious stimuli (51°C radiant heat, 8-sec duration) were focused on the center of the cell's receptive field (only cells with receptive fields on the glabrous skin of the hindpaw were studied). Noxious stimuli were repeated every 3 min (control studies demonstrated no sensitization or fatiguing of the response). Only noxiously evoked activity was studied. In each animal, only one cell, one route of administration, and one dose of drug was evaluated. Fifteen animals were used for spinal administration, 11 animals for intravenous administration.

Spinal Administration

After control studies, the normal saline that had bathed the spinal cord was carefully removed and replaced by the drug solution. The drug solution (25 μg (n = 6) or 50 μg (n = 9) of alfentanil in 0.5 ml of saline) was gently dropped onto the surface of the spinal cord through a 27-gauge needle. The dura mater and bone had been prepared so that they formed a natural trough that kept the drug solution on the spinal cord while simultaneously keeping it away from the exposed muscle. The spinal cord was carefully watched, and if the level of fluid in the cord decreased, allowing exposure to air, additional drug-free saline was applied.

Subsequent to spinal alfentanil administration, spontaneous and evoked activity were recorded every 3 min for a minimum of 30 min. In two cats, naloxone, 0.1 mg, was given intravenously at 31 min after alfentanil administration. In all other animals, spontaneous recovery from alfentanil suppression was observed for as long as possible.

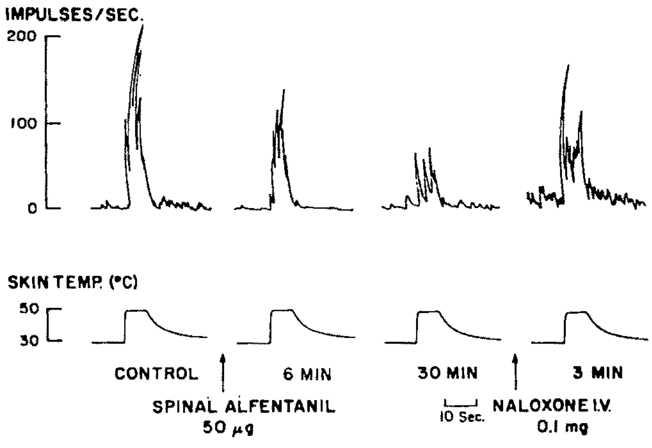

Figure 1. Effects of 50 μg of spinally administered alfentanil on the evoked activity of a single WDR neuron. The lower plots are polygraph tracings of the skin temperature at the center of the receptive field. The upper plots show the evoked activity recorded extracellularly at various times before and after drug administration. Neuronal activity is expressed as impulses/sec. The effect of intravenously administered naloxone, 0.1 mg, is also shown in this figure.

Intravenous Administration

Alfentanil, 12.5 μg/kg (n = 5) or 25 μg/kg (n = 6) (one cell and one dose of drug per animal) was given intravenously over 1 min after control studies. Spontaneous and evoked activity were then recorded every 3 min for a minimum of 30 min. Because of the rapid recovery after intravenous alfentanil, naloxone reversal was not studied.

Data Analysis

Amplitude discrimination was used to electronically isolate the activity of each WDR neuron. The digital output of the amplitude discriminator was integrated and recorded on a polygraph along with an analog representation of skin temperature at the center of each cell's receptive field. The analog temperature

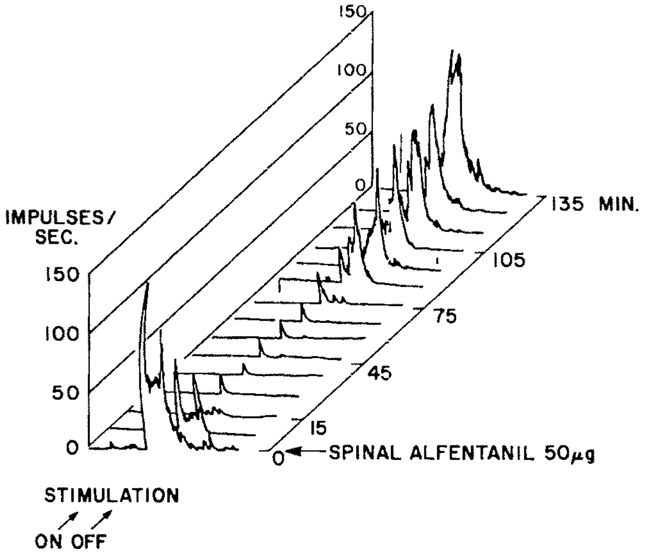

Figure 2. The time course of suppression of a single WDR neuron caused by 50 µg of spinal alfentanil. The abscissa represents time and the ordinate, neuronal firing rate expressed as impulses/sec. Complete recovery was observed approximately 2 hr after alfentanil administration.

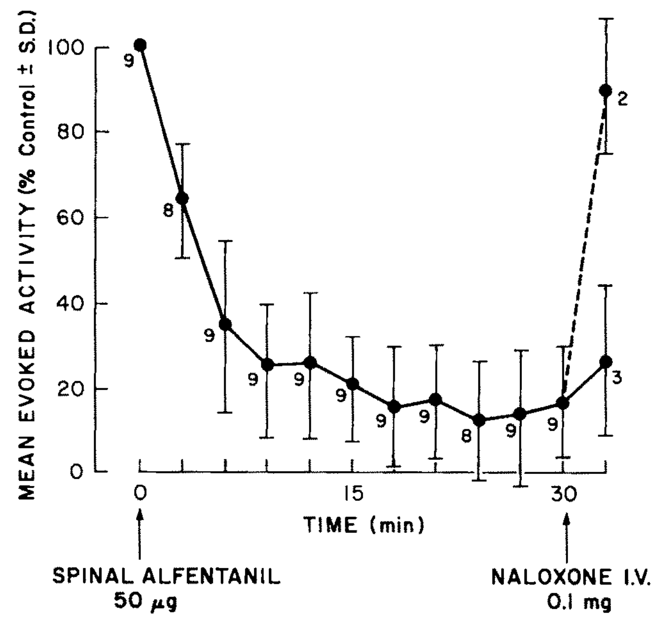

Figure 3. The effects of 50 µg of spinally administered alfentanil on the mean noxiously evoked activity of all neurons studied. The mean evoked activity is expressed as percent of control. The bars indicate ±1 SD. The numbers by the plotted points indicate the number of the cells studied at each time point. The dotted line at 30 min represents naloxone-induced reversal of neuronal activity.

data were converted to a digital signal and, along with the amplitude discriminator output, stored in a DEC PDP 11/40 computer. Data were also recorded on magnetic tape. Markers representing stimulus on and off times were also recorded. On-line data analysis was used to monitor progress during an experiment. All data analysis reported in this paper was computed off-line using a series of software programs developed in-house. The period of stimulus-evoked activity of each neuron in the control state was determined by the off-line analysis using the following criteria. The spontaneous rate 30 sec prior to stimulus onset was calculated. Subsequent to the end of the stimulus, the time at which the firing rate had returned to within 10% of the prestimulus control was determined. That point in time was considered to be the end of stimulus-evoked activity. The period of time from stimulus onset until return of activity to within 10% of prestimulus control was considered to be the period of evoked activity. That period was determined for each neuron and used to normalize the evoked activity of each neuron. Thus, a time normalized measure of evoked activity was available for each stimulus presentation.

Because of the nature of the data, statistical significance was determined by Student's *t*-test. Two things were done in order to avoid the problems of repeated *t*-tests (increased α, type I error). Only *P* values of less than 0.01, rather than 0.05, were considered significant, and a maximum of five tests were performed on any data set. These steps assured that type I error would be no greater than if ANOVA and appropriate post hoc comparisons were used.

Results

Both spinally and intravenously administered alfentanil suppressed noxiously evoked activity of all the WDR neurons studied.

Spinal Administration

The effect of 50 µg of spinally administered alfentanil on the neuronal activity of an individual WDR neuron is shown in Figure 1. During control, the presentation of a 51°C stimulus for 8 sec caused a noticeable activation of this neuron. Six minutes after the spinal administration of 50 µg of alfentanil, the evoked activity was significantly reduced to 67% of control, and, at 30 min, it had been further reduced to 36% of control. This figure also shows the effects of 0.1 mg of intravenously administered naloxone on the alfentanil suppression. At 31 min after alfentanil administration, naloxone, 0.1 mg, was injected intravenously. Three minutes after naloxone administration, the evoked activity had returned to predrug control

Table 1. Summary of Effects of Low-Dose Spinal (25 μg) and Low-Dose Intravenous (12.5 μg/kg) Alfentanil on Mean Noxiously Evoked Activity of WDR Neurons[a]

	Time After Drug Administration				
	6 min	12 min	18 min	24 min	30 min
12.5 μg/kg intravenous	57 ± 11	84 ± 4	93 ± 5	96 ± 10	94 ± 11
25 μg spinal	82 ± 10	74 ± 13	69 ± 14	75 ± 17	84 ± 22

[a] Numbers are percent of control ± SD.

values, although the shape of the response was not the same as in the control situation.

Figure 2 shows the time course of suppression caused by 50 μg of spinally administered alfentanil and spontaneous recovery from the alfentanil effect for a single WDR neuron. Just after drug administration, the evoked activity began to decrease with maximum suppression occurring 30 min after spinal alfentanil administration. The evoked activity gradually recovered spontaneously until approximately 2 hr after drug administration, when the firing frequency of the neuron had returned to the predrug control value.

Figure 3 shows the effects of spinally administered alfentanil on the mean evoked activity of all the cells studied after 50 μg of spinally administered alfentanil. Significant suppression began within 3 min after drug administration. The maximum mean suppression was 86% at 24 min. The reversal of this suppression by 0.1 mg of intravenously administered naloxone is shown in Figure 3 as a dotted line. This naloxone-induced recovery is in contrast to the continued suppression of the cells that were not given naloxone.

Table 1 contains a summary of the effects of the lower doses of spinal (25 μg) and intravenous (12.5 μg/kg) alfentanil on the neurons studied. The effects of 25 μg of spinally administered alfentanil were less than those produced by the 50-μg dose. The maximum mean suppression to 63% of control at 24 min after drug administration was significantly less than the maximum suppression produced by the higher dose.

Intravenous Administration

Figure 4 represents, for a single WDR neuron, the time course of suppression of the noxiously evoked activity and recovery after intravenous alfentanil administration. The mean effects of 25 μg/kg of intravenously administered alfentanil on all the neurons studied are shown in Figure 5. Maximum suppression occurred within 3 min, and the activity of the neurons returned to control values within 30 min. The 25-μg/kg dose produced a significantly greater level of suppression than did the 12.5-μg/kg dose. After the 12.5-μg/kg dose, a maximum suppression to 57% of control was seen at 6 min.

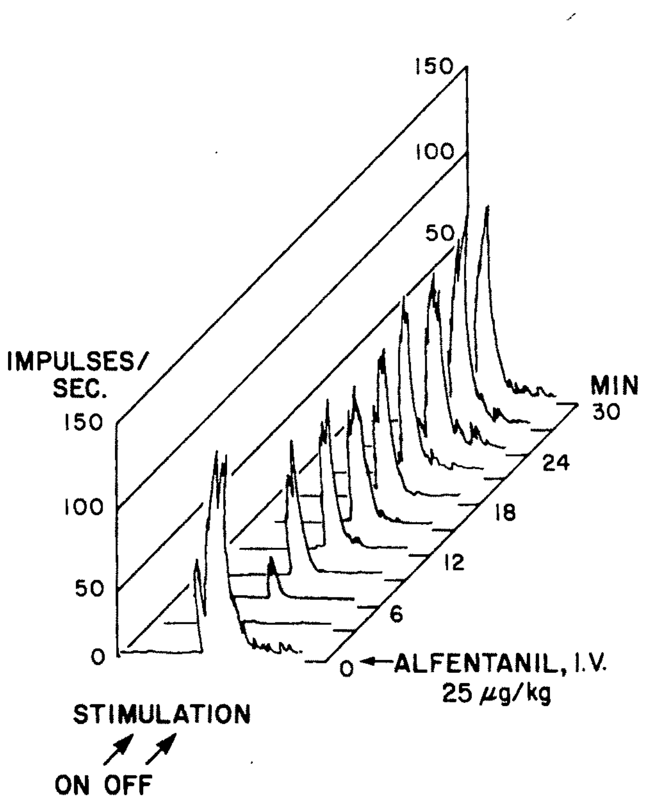

Figure 4. The time course of an intravenously administered dose of 25 μg/kg of alfentanil on a single WDR neuron. The abscissa represents time and the ordinate, neuronal firing rate expressed as impulses/sec.

A comparison of Figures 3 and 5 or Figures 2 and 4 demonstrates the clear difference in onset and duration of effect that resulted from the different routes of drug administration.

Discussion

Alfentanil has been shown, in animal models, to be capable of producing analgesia when administered into the spinal intrathecal space (3). Thus its ability to suppress noxiously evoked activity of WDR neurons would be predicted. The time course and degree of suppression reported in the present study compare favorably with earlier reports of morphine and fentanyl effects in the same preparation from our laboratory. Homma et al. (4) reported that 0.25 mg of spinally administered morphine reduced the mean noxiously evoked activity of WDR neurons to 30% of control within 30 min. Suzukawa et al. (5) reported that 15 μg of spinally administered fentanyl reduced the mean noxiously evoked activity of WDR neurons to within 20% of control within 30 min. In this study, 50 μg of alfentanil had reduced the activity to 18% of

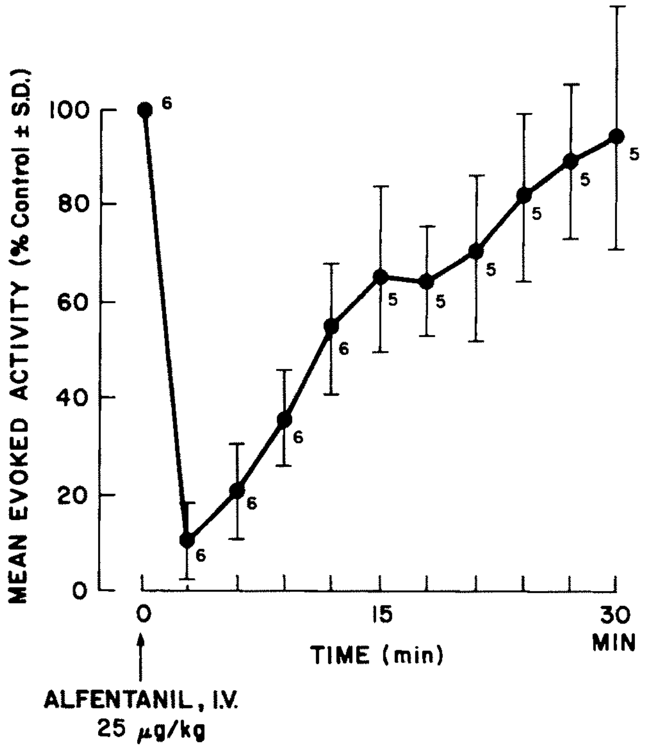

Figure 5. The effects of 25 µg/kg of intravenously administered alfentanil on the mean evoked activity of all neurons studied. The mean evoked activity is expressed as percent of control. The bars indicate ± 1 SD. The numbers by the plotted points indicate the number of the cells studied at each time point.

control at 30 min. The onset of effect was also comparable, with fentanyl producing the most rapid reduction in evoked activity and morphine being the slowest. Although the lower spinal dose of alfentanil produced maximum suppression comparable to that produced by the lower dose of morphine, the alfentanil effect seemed to have a more rapid onset but shorter duration. This may be due to alfentanil's greater lipid solubility. Table 2 presents a summary of the effects of spinally administered morphine, fentanyl, and alfentanil studied in the same animal model in our laboratory.

Alfentanil has a relatively high lipid solubility (log p, partition coefficient, is 2.16, as compared with 0.36 for morphine, personal communication, Janssen Pharmaceutica) while also having a small volume of distribution and a rapid clearance from the body (2). These factors should allow the drug to enter the spinal cord rapidly while minimizing the danger associated with systemic or cerebrospinal fluid redistribution. The duration of effect, however, is short enough that a single administration of alfentanil for spinal analgesia would not produce an analgesia of significant duration when compared with other available drugs (e.g., morphine). Thus although alfentanil clearly should be able to produce a profound spinal analgesia, its use for this purpose might be limited to procedures in which only short periods of analgesia are required or in which repeated administration is not a problem.

Table 2. Comparison of Drug Suppression of Noxiously Evoked WDR Neuron Activity by Spinally Administered Opiates[a]

	6 min	12 min	18 min	24 min	30 min
Morphine[b]					
0.10 mg	92	88	76	64	62
0.25 mg	65	57	44	33	30
Fentanyl[c]					
10 µg	71	63	55	49	47
15 µg	38	34	30	29	22
25 µg	23	11	10	9	11
Alfentanil					
25 µg	82	74	69	75	84
50 µg	36	24	17	15	18

[a] Values are expressed as mean % of control.
[b] From Homma et al., 1983.
[c] From Suzukawa et al., 1983.

One of the exciting developments associated with spinal opioid analgesia has been the long duration of action that can be produced with some drugs. The very short duration of action of alfentanil permitted us, in this study, to graphically demonstrate the difference in kinetics associated with spinal vs intravenous administration. Clearly, the intravenous route of administration is capable of producing an occupancy of spinal receptors (spinal cord transection eliminates descending inhibitory effects) that produces an intense, rapid, and short-lived suppression of WDR neuron activity. Spinal application, in spite of the high lipid solubility of alfentanil, results in a suppression that is both much slower in onset as well as longer in duration, as can be seen by comparing Figures 3 and 5. The degree of difference could not be predicted from the kinetics derived from intravenous administration.

The importance of spinal opioid analgesia extends far beyond the present clinical utilization of this technique for the alleviation of certain types of pain. This technique has made both basic scientists and clinicians increasingly aware of the importance of the pharmacology of the spinal cord as it relates to sensory modulation. The intricacies and potential future clinical importance of spinal cord pharmacology as it relates to pain cannot, at the present time, be overemphasized. It is important to remember that as future developments arise for the spinal administration of drugs for the alleviation of pain, it will be essential to study the kinetics occurring after that route of administration. As is clearly demonstrated in this study, and as has been well documented by many other clinicians and basic scientists, the spinal route of drug administration imposes barriers and regulatory mechanisms to the movement of drugs that cannot be readily predicted from data derived after intravenous drug administration.

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The Influence of Diazepam on the Pharmacokinetics of Intravenous and Epidural Bupivacaine in the Rhesus Monkey

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THOMPSON GA, TURNER PA, BRIDENBAUGH PO, STUEBING RC, DENSON DD. The influence of diazepam on the pharmacokinetics of intravenous and epidural bupivacaine in the rhesus monkey. Anesth Analg 1986;65:151–5.

Pretreatment of patients with diazepam has been reported to reduce the plasma half-life of epidurally administered bupivacaine. The concentrations of bupivacaine used to estimate its plasma half-life may be influenced by input into the vascular system (rate and extent of absorption from the epidural space) and disposition (distribution and elimination). We conducted a study in Rhesus monkeys in which the input function was known and the influence of intravenous diazepam on the disposition of intravenous bupivacaine could be delineated. Results indicated no differences in the primary pharmacokinetic parameters (i.e., total clearance and volume of distribution) for the disposition of bupivacaine. To determine whether the apparent disparity between these results and a previous study might be due to a diazepam-induced alteration in the input function, the influence of intravenous diazepam or saline on the mean absorption time of epidurally administered bupivacaine was also studied in monkeys. Epidural bupivacaine was completely absorbed whether the animals received intravenous saline or intravenous diazepam. No significant differences in pharmacokinetic parameters were found between animals pretreated with intravenous saline or intravenous diazepam and receiving an epidural injection of bupivacaine. The mean residence time of bupivacaine in the body ($P < 0.01$) and plasma elimination half-life ($P < 0.005$) were significantly longer after epidural administration than after intravenous administration. Intravenous diazepam does not alter the pharmacokinetics of intravenously or epidurally administered bupivacaine.

Key Words: ANESTHETICS, LOCAL—bupivacaine. HYPNOTICS, BENZODIAZEPINES—diazepam. PHARMACOKINETICS—bupivacaine.

The use of diazepam preoperatively as an anxiolytic, as well as in the management of central nervous system (CNS) toxicity resulting from local anesthetics, is well recognized. In a previous study, intravenous diazepam was shown to significantly decrease the plasma elimination half-life of epidurally administered bupivacaine and etidocaine (1). Because the blood concentration of drug is determined by both input (absorption) and disposition (distribution and elimination), the influence of adjuvant drugs on either of these functions cannot be defined without knowledge of the other (2). Assuming diazepam does not alter input, a reduction in the half-life can be explained by a change in the total clearance (CL), the volume of distribution (V_z) component(s) in the disposition function (3), or both. To accurately examine the influence of intravenous diazepam on bupivacaine disposition, a study must be conducted such that the input is known. Similarly, once the effect, if any, of intravenous diazepam on disposition of bupivacaine is defined, a study can be conducted to evaluate the effect of intravenous diazepam on the bupivacaine input function after its extravascular administration. The purpose of this study was to determine the influence of intravenous diazepam on the disposition function of bupivacaine after intravenous administration (known input) and on the input function (known disposition) after epidural administration using Rhesus monkeys.

Methods

Animal Model

Input and disposition functions for bupivacaine were studied in six adult Rhesus monkeys. A 2 × 2 ran-

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domized complete block design, separated by a 5-week rest period, was used for each route of administration. After an overnight fast, monkeys were sedated with ketamine (10 mg/kg intramuscularly). Under light general anesthesia (7:3 L N_2O:O_2 with 0.5% halothane), cannulae were placed in a peripheral leg vein for administration of drugs and maintenance fluids (lactated Ringer's solution containing 5% dextrose) and in a saphenous or radial artery for blood sampling. Systolic, diastolic, mean arterial pressure, and heart rate were measured noninvasively with an automated blood pressure monitor (Dinamap Model 1245). Lead II ECG was continuously monitored using a Gross Model 7P6-C electrocardiograph. Animals were allowed to recover from anesthesia in a primate restraining chair before administration of diazepam, bupivacaine, or both.

Intravenous Administration

Diazepam (0.1 mg/kg) or saline was administered intravenously over 1 min, followed 10 min later by bupivacaine, 1 mg/kg, infused over a 1-min period. Four-ml arterial blood samples were collected at 4, 7, 10, 15, 20, 25, 30, 45, 60, 90, and 120 min after completion of the intravenous injection of bupivacaine, and then every hour for a total of 8 hr. Blood removed by sampling was replaced with normal saline (3 ml per 1 ml blood).

Epidural Administration

After placement of the arterial and venous cannulae, the animals were placed in the right lateral decubitus position. A blunted 20-gauge thin-wall spinal needle was inserted into the epidural space using a midline approach at L4-5 or L5-6 and a loss of resistance technique. After insertion of the catheter (PE-10) into the epidural space, the absence of either blood or CSF in the catheter hub was used as the criteria for correct placement. Gentle aspiration and gravity were used in an attempt to detect the presence of blood and/or CSF in the catheter. Animals were then allowed to recover from anesthesia in a primate restraining chair prior to drug administration, after which diazepam (0.1 mg/kg) or saline was administered intravenously over a 1-min period. Ten minutes later, 15 mg bupivacaine (2 ml of 0.75%) was injected over 1 min through the epidural catheter. Four-ml arterial blood samples were collected 4, 7, 10, 15, 20, 25, 30, 45, 60, 90, and 120 min after completion of the epidural injection of bupivacaine, and then every hour for a total of 8 hr. Blood removed during sampling was replaced with normal saline (3 ml per 1 ml blood).

Table 1. Definitions of Pharmacokinetic Symbols

Symbol	Definition
AUC	Area under the blood concentration–time curve from zero to infinity.
AUMC	Area under the first statistical moment blood concentration–time curve from zero to infinity.
CL	Total body clearance.
D	Dose.
F	Bioavailability of drug after epidural injection.
λ_z	Elimination or terminal disposition rate constant.
MAT	Mean absorption time after epidural injection.
MRT	Mean residence time of drug in the body.
V_{ss}	Steady state volume of distribution.
V_z	Volume of distribution in the elimination phase.

Analysis

Blood samples were allowed to clot, after which serum obtained by centrifugation was stored at −20°C until analyzed within 48 hr. Total bupivacaine concentrations were determined by gas chromatography as previously reported (4,5).

Analysis of Blood Concentration–Time Data

Concentration–time data obtained from the intravenous and epidural studies were analyzed independent of compartment model using statistical moment theory (6). Table 1 is a summary of the pharmacokinetic symbols.

The area under the curve (AUC) and area under the first moment curve (AUMC) were calculated by integration of concentration–time data using the trapezoidal rule (6). Pharmacokinetic parameters were then calculated as follows:

$$F = \frac{(AUC)_{EP}}{(AUC)_{IV}} \cdot \frac{D_{IV}}{D_{EP}} \quad (1)$$

$$CL = \frac{F \cdot D}{(AUC)} \quad (2)$$

$$V_z = \frac{CL}{\lambda_z} \quad (3)$$

$$V_{ss} = CL \cdot MRT \quad (4)$$

$$MRT = \frac{AUMC}{AUC} \quad (5)$$

$$MAT = (MRT)_{EP} - (MRT)_{IV} \quad (6)$$

Statistical Analysis

All data are presented as mean ± standard deviation (SD). Pharmacokinetic parameters for each route of

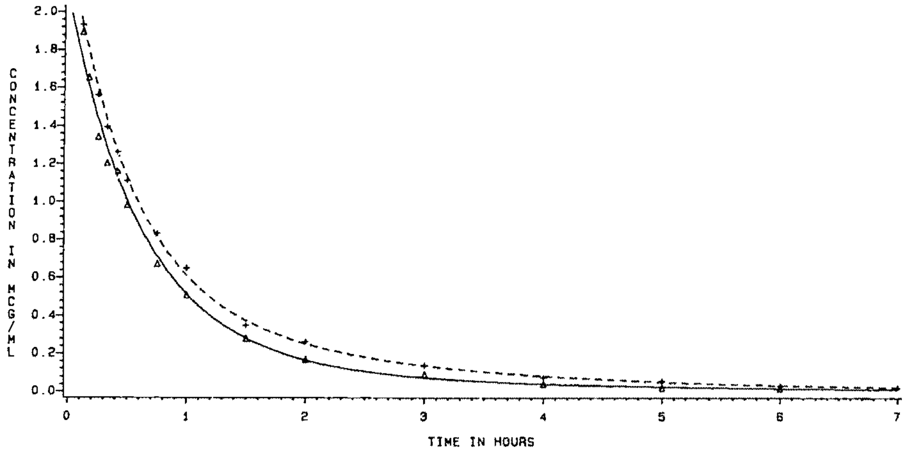

Figure 1. Plots of plasma concentrations of bupivacaine after intravenous injection (1 mg/kg) without (solid line) or with (dashed line) pretreatment with diazepam (0.1 mg/kg).

administration of bupivacaine were compared using a one-within–one-between analysis of variance (7). Differences between routes of administration were analyzed using *t*-test for paired observations. A P value < 0.05 was considered the minimum level of statistical significance.

Results

Although animals pretreated with diazepam appeared to be modestly sedate, no significant differences in respiratory rate, heart rate, systemic diastolic, or mean arterial pressure were found. A typical concentration–time profile for bupivacaine after intravenous administration of bupivacaine in the presence and absence of diazepam is shown in Figure 1. Calculations of pharmacokinetic parameters obtained for bupivacaine after intravenous administration are shown in Table 2. Statistical analysis of the various pharmacokinetic parameters that comprise the disposition function indicate no significant effect of pretreatment with diazepam. Figure 2 is a representative concentration–time profile after epidurally administered bupivacaine with or without diazepam pretreatment. The results of the pharmacokinetic analysis after epidural administration are summarized in Table 3. No significant effect of diazepam pretreatment were found. MRT ($P < 0.01$) and $t_{1/2}$ ($P < 0.005$) were significantly longer after epidural bupivacaine than after intravenous bupivacaine. Bioavailability calculations demonstrate complete absorption of bupivacaine in epidural treatments with or without diazepam pretreatment.

Table 2. The Influence of Intravenous Diazepam (0.1 mg/kg) on the Pharmacokinetics of Intravenously Administered Bupivacaine (1 mg/kg) in Rhesus Monkeys[a]

	Control	Diazepam
Body weight (kg)	9.60 ± 1.34	9.70 ± 1.50
CL (L·kg^{-1}·hr^{-1})	0.60 ± 0.10	0.67 ± 0.20
V_{ss} (L/kg)	0.66 ± 0.16	0.63 ± 0.21
V_z (L/kg)	1.16 ± 0.32	1.49 ± 0.89
$t_{1/2}$ (hr)	1.33 ± 0.29	1.59 ± 0.81
MRT (hr)	1.10 ± 0.24	1.06 ± 0.63

[a] $n = 6$; mean ± SD.

Discussion

Intravenous diazepam has been previously reported to decrease the elimination half-life of epidurally administered bupivacaine (1). We chose the 0.1-mg/kg dose of diazepam to reproduce the premedication dose used by Giasi et al. (1). For accurate estimation of the elimination half-life of any drug, the following conditions must be met (6,8): Blood sampling for drug concentration measurements must be continued for a sufficient length of time, and the influence of the input function on the concentration-time profile must be approaching zero (i.e. $[e^{-ka \cdot t} \rightarrow 0]$) when the elimination half-life is determined graphically. If absorption is not complete at the times selected for assessing the elimination half-life, an accurate estimate cannot be obtained because there are two processes occurring, i.e., drug is still entering as well as being eliminated from the systemic circulation. Thus, such estimates will contain contributions from the absorption and elimination phases.

The reported elimination half-life for bupivacaine after intravenous administration is approximately 3 hr (9). In the present study, the sampling period was selected to accurately characterize the concentration–time profile. By using rapid intravenous administration, the input function was known and was identical when intravenous diazepam was or was not previously administered. Therefore, any difference in the estimated parameters must be ascribed to a di-

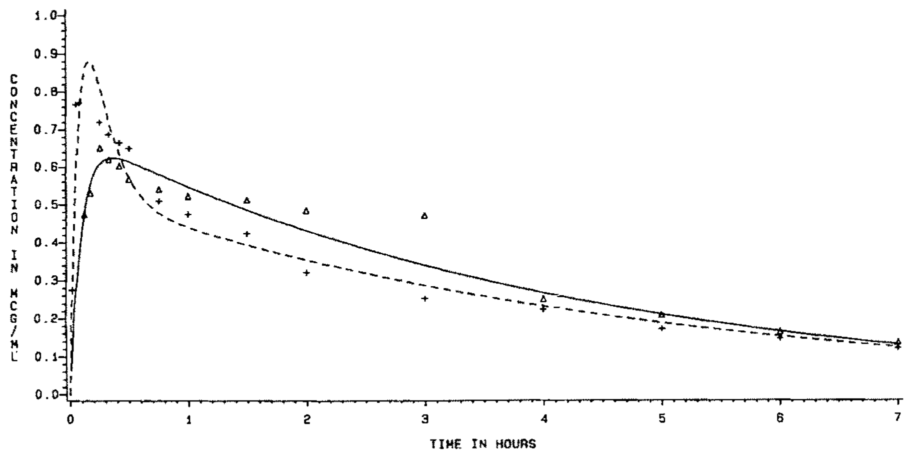

Figure 2. Plots of plasma concentrations of bupivacaine after epidural administration (15 mg) without (solid line) or with (dashed line) pretreatment with diazepam (0.1 mg/kg).

azepam-induced alteration in the disposition of bupivacaine.

The elimination half-life of a drug depends on total clearance and volume of distribution (3). Total clearance is determined by the free fraction of drug, the ability of the eliminating organ to remove the free fraction of drug (intrinsic clearance), and the rate at which the drug is presented to the eliminating organ (blood flow) (10). In those drugs for which the extraction ratio by the eliminating organ is low, as with bupivacaine, total clearance becomes a function of the free fraction and intrinsic clearance. In general, the volume of distribution of a drug is determined by its binding at plasma and tissue sites, and by the volume and pH of the various body fluids (11). For bupivacaine, the major determinant of its distribution is tissue binding, because greater than 90% of the drug is bound to tissue sites (12).

A reduction in the elimination half-life of a drug must be due to an increase in total clearance or a reduction in volume of distribution. In order for bupivacaine total clearance to be increased, either the free fraction or the intrinsic clearance must be increased. A recent study has shown that protein binding of bupivacaine is not affected by diazepam (13). Therefore, the only possibility is an increase in the intrinsic clearance of bupivacaine (i.e., an increase in metabolic rate). For the volume of distribution to be decreased, a decrease in the tissue binding must occur. For bupivacaine, whose therapeutic index is small, a decrease in tissue binding would result in a transient increase in free fraction and could result in an increased risk of toxicity.

In the present study, the disposition function of bupivacaine is unaltered in the presence of diazepam, suggesting that diazepam affects neither intrinsic clearance nor tissue binding. Because there is no alteration in tissue binding, concomitant administration of diazepam and bupivacaine should be deemed safe at least from a pharmacokinetic point of view.

Table 3. The Influence of Intravenous Diazepam (0.1 mg/kg) on the Pharmacokinetics of Epidurally Administered Bupivacaine (2 ml of 0.75% Solution) in Rhesus Monkeys[a]

	Control	Diazepam
Body weight (kg)	9.80 ± 1.40	9.73 ± 1.43
CL ($L \cdot kg^{-1} \cdot hr^{-1}$)	0.59 ± 0.12	0.63 ± 0.35
$t_{1/2}$ (hr)	3.05 ± 0.92	3.52 ± 1.03
MRT (hr)	3.59 ± 1.26	4.52 ± 1.55
MAT (hr)	2.49 ± 1.37	3.71 ± 1.39
F	1.06 ± 0.26	0.93 ± 0.23

[a] $n = 6$; mean ± SD.

Mean absorption time and total clearance after epidural administration of bupivacaine were unaffected by pretreatment with intravenous diazepam. Thus diazepam does not affect the input function for bupivacaine. The elimination half-life of bupivacaine was significantly longer after epidural administration than after intravenous administration. This is consistent with the data of Tucker and Mather, who demonstrated a biphasic absorption process after epidural administration of bupivacaine in humans (14). The slow absorption phase precludes accurate measurement of the elimination rate, even when sampling is conducted over three half-lives of the drug. The slow absorption phase after epidural administration is of clinical relevance because alterations in this phase govern the extent of drug accumulation when multiple injection techniques are being used. The biphasic nature of the absorption function does not allow one to estimate the absorption rate accurately using either classical pharmacokinetic models or statistical moment theory. V_{ss} and V_z after epidural administration cannot be reliably calculated because an accurate estimation of both absorption and elimination rates is required.

It is important to remember that drug interactions may be of several types and alterations in the apparent elimination half-life may be due to corresponding changes in total clearance, volume of distribution, or both, and also to alterations in the absorption process if absorption is rate-limiting. Such changes in the rate and extent of absorption are often not appreciated and consequently overlooked.

The choice of the statistical analysis for the present study was made to minimize errors in repeated measures which are due to interanimal differences. By using the one-with–one between analysis, errors associated with interanimal differences are subtracted from the comparison calculations allowing a maximum likelihood of detecting differences in pharmacokinetic parameters due solely to diazepam. This analysis is also designed to detect differences due to the order in which the treatments were administered. Similarly, the AUC approach allows the use of "raw" concentration-time data rather than exponents and coefficients resulting from a nonlinear regression analysis of the data. This design and analysis are extremely important when a small number of subjects are involved because using a standard analysis of variance would result in a low probability that small but significant differences would be detected.

The present data demonstrate that diazepam does not alter the absorption or disposition pharmacokinetics of bupivacaine after bupivacaine is administered either intravenously or epidurally. The apparent conflict between the current study and the previous report that diazepam does affect the pharmacokinetics of epidurally administered local anesthetics in humans (1) is due in part to the significant intersubject variation encountered in the human study. In the present study, this was resolved by using a crossover design, an option not ethically available in human studies.

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Does Intravenous Infusion of Nitroglycerin Potentiate Pancuronium- and Vecuronium-Induced Neuromuscular Blockade?

Sylvia Schwarz, MD, Sandor Agoston, MD, PhD, and Martin C. Houwertjes

SCHWARZ S, AGOSTON S, HOUWERTJES MC. Does intravenous infusion of nitroglycerine potentiate pancuronium- and vecuronium-induced neuromuscular blockade? Anesth Analg 1986;65:156–60.

The dose requirement for 95% depression of twitch tension and the time course of the neuromuscular blocking effects of the ED_{95} *of pancuronium bromide and vecuronium bromide were studied during intravenous infusion of glucose, 5%, and nitroglycerin, 1* $\mu g \cdot kg^{-1} \cdot min^{-1}$*, in 20 cats anesthetized with pentobarbital. Nitroglycerin administered continuously starting 1 hr before the administration of the* ED_{95} *and maintained during at least five maintenance doses of either pancuronium or vecuronium did not significantly potentiate the action of the neuromuscular blocking drugs, nor did it alter their time course of action. A tendency for a decrease (statistically not significant) rather than an increase in the duration of action of maintenance doses of both pancuronium and vecuronium was apparent during the treatment with nitroglycerin. These findings indicate a lack of interaction between pancuronium or vecuronium and nitroglycerin, provided that moderate doses are used.*

Key Words: DRUG INTERACTIONS—nitroglycerine. NEUROMUSCULAR RELAXANTS—pancuronium bromide, vecuronium bromide. PHARMACOLOGY—nitroglycerine.

Nitroglycerin (NTG) has been known as the mainstay of symptomatic treatment for angina pectoris for more than 100 yr. However, more recently, new uses have been found for intravenously administered NTG in the treatment of myocardial ischemia both during coronary revascularization surgery and perioperative hypertension, as well as during general anesthesia as a deliberate hypotensive agent.

Early clinical observations with intravenously administered NTG prompted Glisson et al. (1) to study the interactions of this drug with neuromuscular blocking agents in animals. They found that intravenous infusion of NTG begun 1 hr prior to the administration of the neuromuscular blocking drugs significantly prolonged the duration of pancuronium-induced neuromuscular blockade in the cat. Surprisingly, in the same study the NTG treatment appeared to have no effect on the time course of action of *d*-tubocurarine or succinylcholine. With the emergence of vecuronium bromide (Org NC 45), a monoquaternary analogue of pancuronium (2), the interaction of this new drug with intravenous NTG became clinically important. This prompted us to undertake the present study with the aim of determining the effects of intravenous NTG on the time course of vecuronium-induced neuromuscular blockade in the cat, using pancuronium as a reference compound.

Methods

Experimental Preparation

A total of 20 adult cats (2.5 ± 0.9 kg) of either sex were anesthetized with pentobarbital sodium (40 mg/kg intraperitoneally plus maintenance doses of 4 mg/kg intravenously). After orotracheal intubation, artificial ventilation with air through a cuffed Magill tube of 5.5 mm external diameter was maintained with a Hoek Loos MK II (Amsterdam) infant respirator at a rate of 30 beats/min and a tidal volume of 18 ml/kg. Ventilation was monitored by a capnograph (Gould Mark II) and the end tidal CO_2 was kept at 3.5 ± 0.45%. Heart rate, ECG (Pulse Monitor, MS-35; Electrodyne Co. Inc., USA), and mean arterial blood pressure (Statham P23D6 transducer, KWS 3085 HSE Electromanometer) were monitored throughout the experiment. Body temperature was kept constant at 36–37°C by heating the operating table. Rectal temperature was measured with a thermistor (Electrola-

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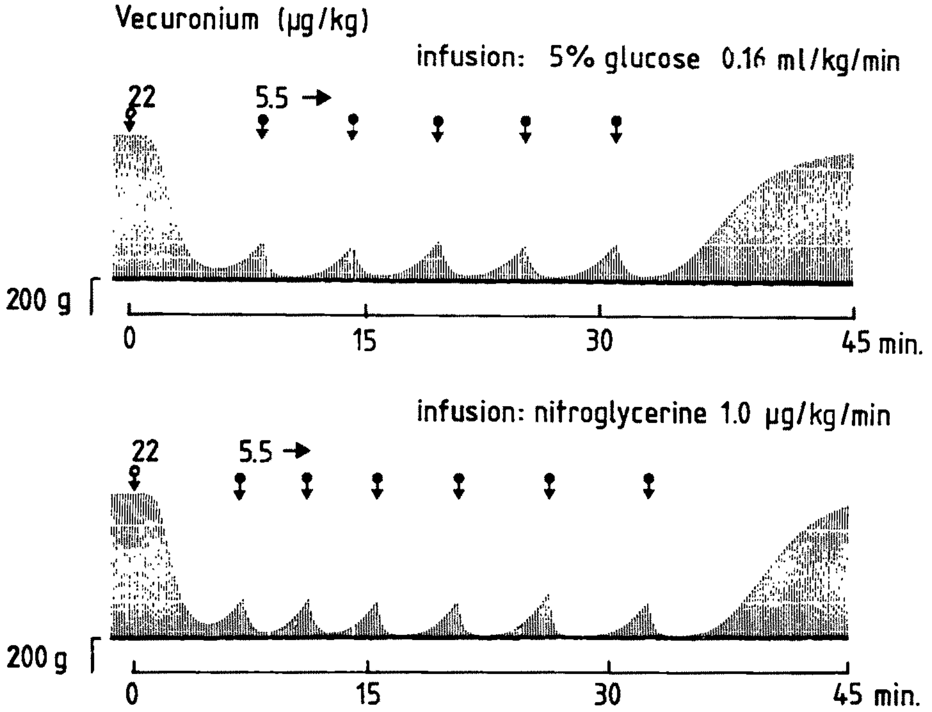

Figure 1. Time course of the neuromuscular blocking effects of vecuronium (initial dose ↓ of 22.0 µg/kg and several maintenance doses ↓ 5.5 µg/kg) in the tibialis anterior muscle preparation in the cat. The two experiments were performed in the same animal 1 hr apart. In the first study (upper trace) glucose, 5%, was administered, whereas in the second experiment (lower trace) nitroglycerin, 1.0 µg·kg^{-1}·min^{-1}, was administered by intravenous infusion. The infusions started 60 min before the administration of vecuronium and were stopped after complete recovery of the twitch tension after the last maintenance dose.

borit, Copenhagen). The evoked isometric twitch tension (resting tension 200 g) of the tibialis anterior muscle elicited by supramaximal square wave stimuli (applied to the common peroneal nerve) of 0.2-msec duration at a frequency of 0.1 Hz (Grass S88 stimulator, SIU 5 stimulus isolation unit) was continuously recorded via a load cell (UL4-20, Statham) attached to a force displacement transducer (UC3 Gold Cell, Statham) and an MFE two-channel polygraph. The signal was amplified by a Hottinger–Baldwin amplifier (Messtechnik, Darmstadt).

Experimental Procedure

After the induction of anesthesia and intubation of the trachea, ten animals (control group) received a continuous infusion of glucose, 5%, and another group of ten cats (NTG group) received nitroglycerin at a rate of 1 µg·kg^{-1}·min^{-1} through a polythene cannula inserted in the external jugular vein. In all experiments the intravenous infusion (0.16 ml·kg^{-1}· min^{-1}) was started 60 min prior to the administration of the neuromuscular blocking drug and lasted until the end of the experiment. Each of the two groups were further subdivided into two groups of five animals, each receiving either pancuronium ($n = 5$) or vecuronium ($n = 5$). In each experiment 95% depression of the twitch tension was achieved by administration of the individual ED$_{95}$ dose of the neuromuscular blocking agent. The ED$_{95}$ doses for both pancuronium and vecuronium were determined in earlier experiments (not reported here).

In the present study we aimed at producing 95% twitch depression in each single experiment by titrating the dose of the neuromuscular blocking agents under study. In each experiment the standard ED$_{95}$ dose (found in earlier studies in this laboratory) was administered. Occasionally a small additional dose of relaxant had to be given when the standard ED$_{95}$ dose produced less than 95% twitch height depression. With both compounds only those experiments with an initial neuromuscular block of 95% were included.

After the administration of the initial (ED$_{95}$) dose of the neuromuscular blocking agent, five maintenance doses (1/4 of the initial dose) were given whenever the twitch tension returned to 25% of control. The onset time (time taken to reach maximum depression of twitch tension), duration of action of initial dose (the time between the end of the injection of the initial dose and the recovery of twitch tension to 25% of control), duration of maintenance doses (time required for return of the twitch tension to 25% recovery after each maintenance dose), and recovery index (time from 25 to 75% recovery of control twitch tension after the last maintenance dose), as well as the total dose required to produce 95% depression of the twitch tension, were calculated and compared in all four groups.

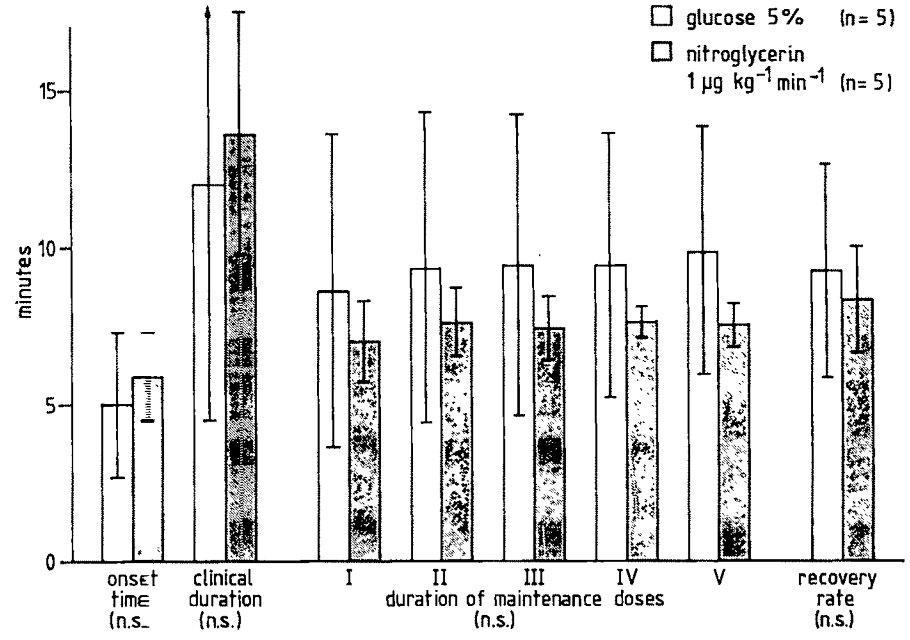

Figure 2. Time course (min, mean ± SD) of the neuromuscular blocking effects after the ED_{95} and five maintenance doses of pancuronium during intravenous infusion of glucose, 5% ($n = 5$), and nitroglycerin in the cat ($n = 5$). Abbreviation: (n.s.), not significant.

In a separate experiment the time course of vecuronium action (ED_{95} dose plus maintenance dose) was compared during the intravenous infusions of glucose, 5%, and nitroglycerin, 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, in the same animal ($n = 1$). The two experiments were performed in succession 1 hr apart. Statistical analysis was performed by Student's t-test for unpaired values. P values less than 0.05 were considered statistically significant. All values are expressed as mean ± 1 SD.

Results

No statistically significant difference could be proven in the dose requirement for 95% depression of the twitch tension of either neuromuscular blocking drug after a 1-hr intravenous infusion of either glucose, 5%, or nitroglycerin, 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The ED_{95} doses in the control group and in the NTG group were 32.0 ± 2.5 µg/kg and 34.0 ± 3.8 µg/kg ($P > 0.05$) for pancuronium and 36.5 ± 11.0 µg/kg and 33.0 ± 8.6 µg/kg ($P > 0.05$) for vecuronium, respectively.

The lack of effects of nitroglycerin on both the magnitude and the time course of the neuromuscular blockade produced by vecuronium is also demonstrated in a representative experiment in which the two infusion treatments were combined in the same animal (Fig. 1). The effect of pretreatment with glucose, 5%, vs NTG on the time course of action of pancuronium (initial ED_{95} dose followed by five maintenance doses) is shown in Figure 2. The onset times were 5.0 ± 2.3 and 6.0 ± 1.4 min. The clinical durations were 12.0 ± 7.5 and 13.6 ± 3.8 min. The mean duration of the maintenance doses ranged between 8.6–9.6 min and 7.0–7.6 min. The recovery indices were 9.2 ± 3.4 and 8.3 ± 1.7 min. All values given refer to the control group and NTG group, respectively.

The time course of action of equipotent initial and maintenance doses of vecuronium under the same experimental conditions is shown in Figure 3. In the experimental groups pretreated with glucose, 5%, or NTG, 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, the onset times were 5.0 ± 1.3 and 5.0 ± 1.0 min. The clinical durations were 9.6 ± 3.0 and 9.3 ± 4.0 min. The mean duration of the maintenance doses ranged between 5.4 and 6.6 min and 5.7 and 6.2 min. The recovery indices were 6.8 ± 3.5 and 5.3 ± 2.1 min. All values given refer to the control group and the NTG group, respectively.

Both the heart rate and mean arterial pressure showed fluctuations during the experiments. However, these changes in the NTG group remained within 15% of the control values.

Discussion

The results of the present study indicate that nitroglycerin, 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, administered by intravenous infusion does not enhance the neuromuscular blocking effects of either pancuronium or vecuronium, nor does it alter the time course of effects of the above two compounds in the cat. In contrast to earlier observations (1) our results show a tendency to a

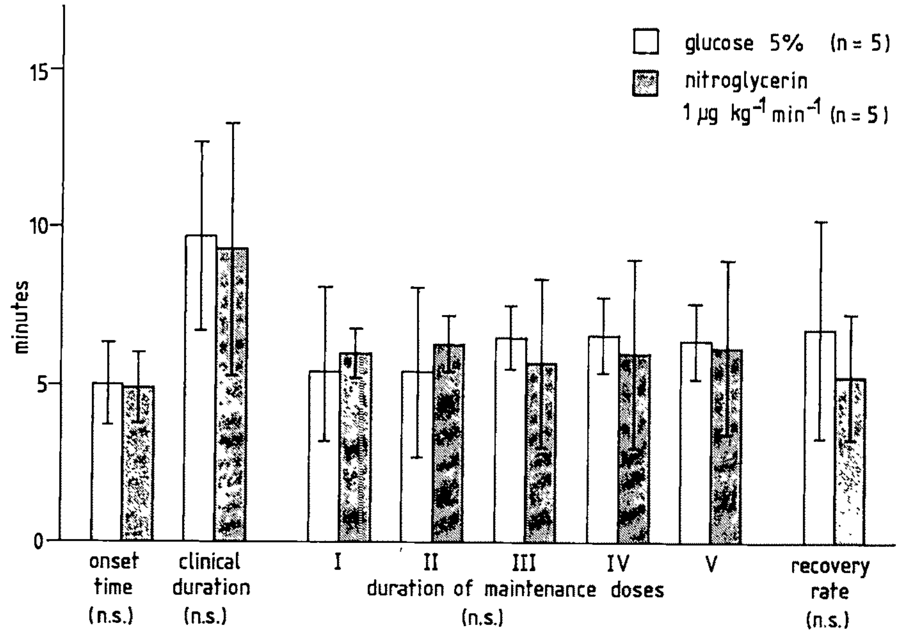

Figure 3. Time course (min., mean ± S.D.) of the neuromuscular blocking effects following the ED$_{95}$ and five maintenance doses of vecuronium during intravenous infusion of glucose 5% (n = 5) and nitroglycerin in the cat (n = 5). Abbreviation: (n.s.), not significant.

shortening of the time course of effects of both pancuronium and vecuronium in animals treated with nitroglycerin. This tendency is shown in Figure 1. The time course of vecuronium action tends to be shorter during the infusion of nitroglycerin in spite of the fact that in the above period the ED$_{95}$ and six maintenance doses of vecuronium were administered for the second time to the same animal.

In contrast to our results obtained with pancuronium, Glisson et al. (1) found that even lower doses of nitroglycerin (0.5 μg·kg^{-1}·min^{-1}) significantly prolonged the duration of action and the recovery rate of pancuronium-induced neuromuscular block, whereas there was no effect on the time course of action of *d*-tubocurarine or succinylcholine. The most likely explanation for this surprising observation may be the use of nonequipotent doses of the above three compounds. In earlier studies in chloralose-anesthetized cats, the calculated ED$_{90}$ doses of *d*-tubocurarine, pancuronium, and succinylcholine were 300–370 μg/kg (3,4,5), 24–30 μg/kg (3,6), and approximately 90 μg/kg (5), respectively. From this it follows that in the above study (1) the ED$_{90}$ doses of *d*-tubocurarine, five times the ED$_{90}$ dose of pancuronium, and the ED$_{50}$ dose of succinylcholine were employed. Therefore it is not surprising that the potentiation by nitroglycerin occurred only in the group treated with pancuronium. The interaction between nitroglycerin and succinylcholine in the cat might be further complicated by the depolarizing mode of action of succinylcholine and by the species-bound low butyril cholinesterase activity (7), which results in a slower rate of hydrolysis of this compound in this species.

In order to create experimental conditions closer to clinical practice, we modified the experimental design used by Glisson et al. (1). For this reason we used a barbiturate for anesthesia instead of α-chloralose and employed a stimulation frequency of 0.1 Hz instead of 0.2 Hz. More importantly, we used moderate equipotent doses of vecuronium and pancuronium instead of overdoses. A single bolus dose of pancuronium of 126 μg/kg (1) is approximately three times the ED$_{90}$ dose of this compound in man, which is seldom necessary under clinical conditions. We conclude that nitroglycerin does not alter the neuromuscular blocking effects of vecuronium and pancuronium in the cat, provided that moderate doses are used.

The authors thank Dr. F. J. Richardson for criticism and Mrs. R. Carpay for secretarial assistance in the preparation of the manuscript.

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Masseter Muscle Rigidity and Malignant Hyperthermia Susceptibility

Henry Rosenberg, MD, and Jeffrey E. Fletcher, PhD

ROSENBERG H, FLETCHER JE. Masseter muscle rigidity and malignant hyperthermia susceptibility. Anesth Analg 1986;65:161–4.

Seventy-seven patients who developed masseter muscle rigidity (MMR) after receiving succinylcholine to facilitate tracheal intubation were evaluated for malignant hyperthermia (MH) susceptibility by in vitro halothane and caffeine contracture tests. Thirty-nine patients were diagnosed as MH-susceptible. Neither age, sex, nor type of surgery or anesthesia distinguished MH-susceptible from nonsusceptible patients. Two susceptible and two nonsusceptible patients had evidence of a myopathy. Fifty-two patients had serum creatine phosphokinase (CPK) levels measured in the perioperative period. Although all values were above normal, CPK values equal to or greater than 20,000 IU within 24 hr of trismus (in the absence of myopathy) were observed in six of 30 patients diagnosed as MH-susceptible, but were found in none of the nonsusceptible patients. Considering the high percentage of patients exhibiting MMR that are indeed susceptible to MH (~50%) compared to estimates of MH in the population as a whole (~0.005%), MMR should be considered a presumptive sign of MH. Perioperative CPK values greater than 20,000 IU are highly suggestive of MH susceptibility. Patients exhibiting MMR should be evaluated for MH susceptibility and myopathies. Succinylcholine should be avoided for subsequent anesthetics in patients with a history of MMR.

Key Words: HYPERTHERMIA, MALIGNANT.

Masseter muscle rigidity (MMR) is a relatively common clinical problem. For example, Schwartz et al. reported that MMR occurred in about 1% of children after halothane induction and succinylcholine administration (1). Because of the association of MMR with malignant hyperthermia (MH), it has been recommended that if trismus is observed anesthesia should be discontinued and the patient investigated for susceptibility to MH (2,3,4). However, the most widely accepted test for MH susceptibility involves a test that is available at only a limited number of centers (5).

The purpose of this study was to determine the coincidence of MMR after succinylcholine with MH susceptibility based on the contracture response of biopsied muscle to halothane and to caffeine; to determine whether any clinical or laboratory findings other than contracture tests are predictive of MH susceptibility; and to describe the association of MMR with other muscle disorders.

Methods

Seventy-seven patients who developed jaw muscle rigidity after succinylcholine administration were evaluated, 33 of whom were included in a previous report (6). The patients were referred for evaluation by practicing anesthesiologists based on clinical evidence of MMR. Information concerning the clinical source and pertinent data was obtained from chart review, patient examination, and referring physicians. All patients received succinylcholine before developing MMR.

The procedure for the muscle biopsy has previously been described (6,7). Fourteen muscle biopsies were obtained with patients under general anesthesia with nontriggering agents and without dantrolene premedication. The remaining 63 biopsies were obtained using femoral and lateral femoral cutaneous nerve block with 1–1.25% mepivacaine and supplemental sedation as necessary (7).

In brief, the vastus lateralis was clamped in situ. Strips of muscle weighing 50–150 mg were dissected and placed in a 37°C bath of modified Krebs solution continuously bubbled with 95% O_2–5% CO_2. The minimum biopsy size had at least six fiber bundles that could be isolated undamaged except for the cut ends. If possible we tested eight fascicles for each patient. The muscle from all patients but one was stimulated

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Table 1. Findings Associated with Masseter Rigidity after Succinylcholine

	MH Positive[a]	MH Negative[a]
Age (yr)	11.9 ± 1.5	10.3 ± 1.2
Sex (male:female)	19:20	15:23
Type of surgery		
Ear, nose, throat	13	19
Eye	2	3
Orthopedic	1	6
Other	22	11
CPK (IU) within 24 hrs of MMR		
Males	8094 ± 3287 (n = 17)	5917 ± 1346 (n = 14)
Females	15,190 ± 4835 (n = 13)	4412 ± 1040 (n = 8)
Males and females	11,169 ± 2828	5344 ± 919

All values expressed as mean ± SEM.

[a] By halothane and caffeine contracture testing.

supramaximally at 0.2 hz with a pulse duration of 2–10 msec. After an equilibration period of several minutes, halothane was added to the gas stream of some preparations. Halothane concentration in the gas phase was verified using gas chromatography. After halothane exposure, preparations were washed, equilibrated 30 min, and then exposed to incremental doses of caffeine (0.125–16mM) added at 2-min intervals or until the contracture had reached a plateau. Patients were considered MH susceptible if any one preparation developed >0.5 g contracture on exposure to 2% halothane or less, >0.7 g contracture to 3% halothane or >0.3 g contracture upon exposure to 2mM caffeine.

Data were analyzed by a two-tailed grouped t-test at a level of $P < 0.05$, comparing MH susceptibles to nonsusceptibles unless otherwise noted.

Results

Each patient underwent a single muscle biopsy. In most cases 6–8 muscle strips were isolated from each biopsy and tested for sensitivity to halothane. The response to halothane was not necessarily uniform for all the muscle strips isolated from a single biopsy. In all, only 86 (54%) of 166 muscle strips from the 39 patients diagnosed as MH susceptible by the contracture test met the criteria for a positive test when exposed to halothane. None of the 159 strips from the 38 patients diagnosed as nonsusceptible met the criteria for MH on in vitro testing. In 11 of the 39 patients diagnosed as MH susceptible, fewer than 25% of the strips tested met the criteria for a positive response to halothane. A similar variability in the response to caffeine was observed. For the 39 MH susceptible patients, a total of 22 (28%) of 80 strips tested met the criteria for MH susceptibility. Sixty-seven strips were exposed to caffeine in the nonsusceptible group, and none exhibited a response typical of MH muscle.

The anesthetic associated with MMR was induced with thiopental in eight of the 39 MH susceptible and in three of the nonsusceptible patients. Anesthesia in the remainder was induced with halothane or enflurane. Occurrence of MMR was induced by succinylcholine in all cases. There were no differences between susceptible and nonsusceptible patients in type of proposed surgery, age, or sex (Table 1), or type of anesthesia used. The most common surgical procedures were tonsillectomy and adenoidectomy.

Five of 39 MH susceptible and 7 of 38 MH nonsusceptible patients had premature ventricular contractures during or after masseter rigidity, a difference that was not significantly different. One patient who later proved to be MH susceptible had an intraoperative increase in temperature to 41°C. There were no other significant differences between intra- and early postoperative temperatures between groups. There were no differences in arterial blood gas tensions between groups when measured in the perioperative period.

The results of myoglobinuria testing were not recorded for all the patients. However, in those patients for which it was recorded, myoglobinuria was present in four of 13 MH susceptible and three of 14 nonsusceptible patients. More specific signs of muscular disorders were also found. For example, central core disease was diagnosed in one susceptible patient and myotonia congenita in another; one case of Becker's dystrophy and one of arthrogryposis (possible fetal alcohol syndrome) were found among the nonsusceptible patients. Aside from the specific changes noted above, nonspecific changes (variation in fiber size, type I fiber predominance, angulated fibers) or normal findings were noted with equal frequency when comparing the histological findings of all susceptible and nonsusceptible patients (manuscript in preparation).

Creatine phosphokinase (CPK) values after MMR were elevated in the 52 patients in whom CPK was measured. Of those patients who were diagnosed as positive, six patients of 30 (20%) had CPK values above 20,000 IU. None of the patients diagnosed as nonsusceptible had CPK values above 20,000 IU. This was statistically significant at a level of $P < 0.05$ by the test for significance between two proportions. One MH negative patient had a CPK after MMR of greater than 50,000 IU, but he proved to have Becker's muscular dystrophy and therefore was excluded from the analysis.

Discussion

Masseter rigidity is relatively common, almost 1%, in the pediatric population when halothane and succinylcholine are used together (1). Trismus after succinylcholine is one of the most frequent early signs of MH and therefore reason for considering the diagnosis of MH. Approximately 30% of the 250 patients referred for biopsy to our center were referred because of MMR, which is similar to the experience of Ellis and Halsall (3). In the present study there was a coincidence of 51% between MMR and MH susceptibility, which is consistent with findings in our preliminary study (8). Similarly, Ellis and Halsall found the coincidence of MMR and MH susceptibility to be 64% using halothane and caffeine contracture testing (3). Flewellen and Nelson (4) report a similar coincidence of MH with MMR; however, their figure was derived by including phenotype K, a group that does not respond to 3% halothane alone but has an accentuated response to halothane and caffeine together. The clinical significance of the phenotype K has not been established. Using our criteria, only two of 18 patients in their study were susceptible to MH. We are unable to explain the apparent discrepancy between our study and that of Flewellen and Nelson except that their population sample size was considerably smaller not only than ours but also that of Ellis and Halsall (3). Also, the mean age (~ 7.5 yr) was lower than in the present study. In contrast to all the above studies, all 12 patients tested for MH susceptibility after MMR in the study by Schwartz et al. were found to be MH susceptible (1). However, this anomaly is most likely related to the use of the calcium uptake assay used to diagnose MH susceptibility, a test the reliability of which has been questioned (5).

There appears to be an abnormally high incidence of myopathies in patients referred for testing due to MMR. Ellis and Halsall (3) noted a concomitant myopathy in seven of 36 MH negative patients who experienced MMR. In our study two nonsusceptible patients had myopathies. We also observed central core disease in one patient diagnosed as MH susceptible and myotonia congenita in another MH susceptible patient. Both myotonia congenita and central core disease have previously been reported in patients with MH susceptibility (9,10).

The most striking finding in the present study, a finding not reported previously (8), concerns the use of CPK values for diagnosis of MH. Although all patients who developed MMR had elevated CPK values after MMR, only MH susceptible patients and the one nonsusceptible patient with muscular dystrophy had CPK values equal to or greater than 20,000 IU. Therefore in the absence of myopathy, this laboratory finding is the only predictor for MH susceptibility after MMR other than contracture testing. However, the CPK values alone as predictors of MH are far too insensitive, as 24 patients with CPK values <20,000 tested as MH susceptible by the contracture test. None of the patients in the Flewellen and Nelson study (4) had CPK values >20,000. CPK values were not reported by Ellis and Halsall (3).

That more patients in those we studied did not experience an overt episode of MH, and only one patient developed marked hyperthermia, is probably related to the early discontinuation of triggering anesthetic agents in all cases. The reason that arterial blood gas tension values were not reliable in diagnosing MH probably relates to the effect of hyperventilation and time lapse between MMR and blood sampling.

The explanation for masseter rigidity without MH susceptibility is not clear. One possibility is that the halothane and the caffeine contracture tests are not sufficiently sensitive to detect all MH susceptible patients. Another is that not all patients with MMR are truly MH susceptible. Also possible is that the contracture tests are not reliable, despite strong evidence to the contrary (5,6). Not all strips from a single muscle biopsy specimen respond to halothane and caffeine in a similar manner despite a twitch response >0.5 g to direct electrical stimulation of the muscle. Therefore the test may be subject to sampling errors. Only about one half of the strips in muscle from MH susceptible patients exhibited a significant contracture to halothane and one fourth to caffeine. Thus in order to minimize sampling error, as many muscle strips as possible should be tested. We suggest that a minimum of six strips from each patient be tested with halothane if possible.

It has recently been suggested that a distinction can be made between muscle from MH negative patients who experienced MMR and other MH negatives by exposing the muscle to 50mM succinylcholine prior to halothane exposure (11). Under these conditions, greater contractures are observed in muscle from patients previously experiencing MMR than in muscle from other MH nonsusceptible patients. The patients testing as nonsusceptible for MH, but who respond to halothane after succinylcholine, may correspond to the K phenotype in the Flewellen and Nelson study (4). Further characterization of the in vitro response to the combination of halothane and succinylcholine is necessary before its significance becomes fully apparent. However, the interaction between halothane and succinylcholine might be useful in delineating the pathophysiology of MMR. Certainly these in vitro drug interaction studies (11) strongly argue against the use of succinylcholine in patients with a history of MMR.

Because of the association of MH with MMR, all investigators advise that anesthetics that trigger MH be discontinued after trismus (2,3,4,6). The data are not available to support the contention that anesthesia may be safely continued by switching to nontriggering anesthetics. After MMR, studies should be done to rule out an MH episode, including serial CPK and muscle biopsy. In the absence of clinical MH, there is no consensus for advising dantrolene therapy. If there is not a definitive diagnosis of MH by muscle biopsy or by perioperative CPK >20,000 IU, nontriggering agents should be used for all subsequent anesthetics in patients who have experienced MMR. Those patients who have had MMR but are found to be MH negative by biopsy should not be exposed to succinylcholine.

In conclusion, masseter rigidity after succinylcholine is associated with MH susceptibility about 50% of the time. This is a much higher incidence than in the population as a whole (~ 0.005%). Patients experiencing MMR tend to be young, and all show evidence of rhabdomyolysis. After succinylcholine-induced jaw rigidity, an elevation of CPK >20,000 IU in the perioperative period is indicative of either MH susceptibility or an underlying myopathy.

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Epidural Morphine Provides Postoperative Pain Relief in Peripheral Vascular and Orthopedic Surgical Patients:

A Dose–Response Study

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A randomized double-blind study compared the dose–response relationship of epidural morphine for postoperative pain relief in two groups of patients whose surgical procedures would result in either moderate (femoral–popliteal bypass) or severe (total knee replacement) postoperative pain. Preservative-free morphine sulphate in doses of 0, 2, 5, or 10 mg in a volume of 10 ml saline were administered via lumbar epidural catheters. The epidural morphine was administered 1 hr after the last dose of intraoperative local epidural anesthetic in an effort to achieve a pain-free postoperative course. A significant relationship existed between the dose of epidural morphine and both time to first required pain medication and 24-hr weighted pain score. Five mg epidural morphine provided significant improvement in postoperative analgesia compared with the control in both groups. Further enhancement of analgesia occurred with 10 mg; however, late respiratory depression, demonstrated by an increased resting Pa_{CO_2} *10 hr after administration, was seen only with the 10-mg dose in both surgical groups. Minor complications such as nausea, vomiting, pruritus, and urinary retention were uncommon and did not appear to be related to dose. We found that 5 mg epidural morphine provided long-lasting postoperative analgesia without serious adverse effects after peripheral vascular and orthopedic surgery.*

Key Words: PAIN, POSTOPERATIVE. ANALGESIC—morphine. ANESTHETIC TECHNIQUES—epidural morphine.

The effective management of acute perioperative pain is one of the most sought after goals in anesthesia practice. Parenteral and oral opiates are most often utilized for acute postoperative pain relief. However, when given by these routes, the opiates provide a relatively brief duration of analgesia and lead to numerous side effects such as sedation and respiratory depression.

In 1979, Behar et al. (1) demonstrated that adequate clinical postoperative analgesia could be obtained with relatively small doses of epidural opiates believed to act directly on the opiate receptors in the spinal cord. Since that time, numerous studies have been carried out using epidural administration of opiates in a broad dose range (0.5–20 mg morphine) with varying results (2). Few controlled studies have been done (3–9) and none have determined the effective dose of epidurally administered opiates for patients with different intensities of postoperative pain. Only two of the controlled studies have assessed their ability to provide a continuum of analgesia from the intraoperative period to the immediate (24 hr) postoperative period (4,9). The present double-blind study was instituted in two groups of surgical patients, i.e. patients undergoing femoral–popliteal bypass surgery (moderate postoperative pain) and patients having total knee replacement (severe postoperative pain). The epidural morphine was administered prior to the complete resolution of the long acting epidural local anesthetic block to provide a continuum between intraoperative and postoperative analgesia.

Epidural morphine has been associated with various side effects. However, the precise correlation between dosage, adequate postoperative analgesia, and the frequency of severe side effects such as delayed

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Table 1. Epidural Morphine Dose

	0 mg		2 mg		5 mg		10 mg	
n	8	8	8	8	10	11	9	8
Median age (yrs)	64	63	65	62	61	65	64	63
Sex (M/F)	4/4	4/4	4/4	4/4	6/4	5/6	5/4	4/4
Group	F-P	T-K	F-P	T-K	F-P	T-K	F-P	T-K

Vital statistics of patients in the two study groups (F-P, femoral–popliteal bypass graft, T-K, total knee replacement).

onset of respiratory depression, has not been studied in different types of patients. The present study was designed both to establish a correlation between dose and side effects and to find the effective analgesic dose, if any, of epidural morphine that was devoid of serious side effects.

Methods

Seventy patients of either sex between 21 and 82 yr of age were studied. Two groups of surgical patients were selected based on the severity of their postoperative pain. One group of 35 patients who underwent femoral–popliteal bypass surgery was expected to develop moderate postoperative pain. A second group of 35 patients who had total knee replacements was expected to develop severe postoperative pain. Both groups were given 0 mg (morphine-free saline), 2, 5, and 10 mg of preservative-free morphine sulfate administered in a volume of 10 ml of normal saline. A research pharmacist placed each dose into a numbered vial and held the code in case it should be needed. The vials were numbered sequentially so that the various doses were randomly assigned to patients in both surgical groups using a double-blind protocol. Informed consent was obtained from all patients, and approval was obtained from the Institutional Review Board for Human Studies at the two hospitals involved.

Epidural anesthesia was performed at L2-3 or L3-4 interspace using a 17-gauge Huber-tipped needle and a midline approach. A 20-gauge catheter was inserted into the lumbar epidural space, and epidural anesthesia was induced with either etidocaine, 1.5%, with epinephrine or bupivacaine, 0.75%. Subsequently, doses of 5 ml of 0.5% bupivacaine were given at intervals as needed for surgery, with all patients receiving at least one such dose. One hour after the last local anesthetic dose and after the arrival of the patient at the recovery room, the contents of one of the numbered 10-ml vials was injected epidurally and the catheter removed. Patients were observed for 24 hr. Vital signs (temperature, pulse, blood pressure, and respiratory rate) and qualitative pain assessment using the Linear Analog Pain Scale (10) were recorded by one of the investigators or the hospital nursing staff, none of whom were aware what medication dose had been administered. These measurements were recorded at 0.5, 1, 2, 4, 8, 10, 12, 16, and 24 hr after the injection of epidural morphine. Additional opiate analgesics (morphine, meperidine, dilaudid, tylox) were ordered by the patients' surgeons using their routine postoperative orders. The standard interval for administration was every 4 hr as needed for pain relief. The total amount of additional opiate analgesic required during the 24-hr postoperative period was recorded, as well as the time of its administration.

The need for bladder catheterization was noted in the knee replacement group whereas the vascular surgery group had an indwelling catheter as part of the surgical routine. All occurrences of other possible adverse effects such as nausea, vomiting, and pruritus were noted. A single arterial blood sample was drawn 10 hr after the morphine injection for determination of Pa_{O_2}, Pa_{CO_2}, and pH. It has been shown that the maximum depression of the CO_2 response curve in volunteer studies is present between 6–12 hr after administration of epidural morphine (11).

An IBM 370 computer with an SAS statistical package was utilized for exploratory data analysis, computation of summary statistics, and the Jonckheere Terpstra test (12). This test is for an increasing treatment effect with increasing dose of drug. A probability of less than 0.05 was considered statistically significant.

Results

There were no differences with regard to age or sex among any of the dose groups in the two surgical populations (see Table 1). There was no relationship between the dose of epidural morphine and any changes in postoperative blood pressure, pulse, respiratory rate, or temperature in either surgical group.

The median time to first requested analgetic medication for the four dose groups was 3.8, 13.4, 24.0, and 24.0 hr in the femoral–popliteal group and 2.3,

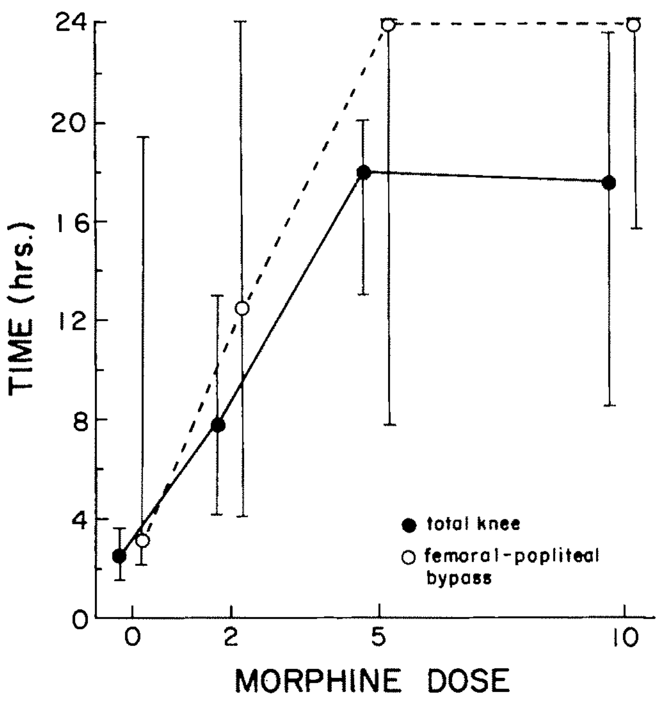

Figure 1. Time to first requested parenteral medication after administration of study drug (median ± quartile). There is a significant relationship between time and dose in both treatment groups ($P < 0.003$) and a significant difference between the two control groups ($P < 0.05$).

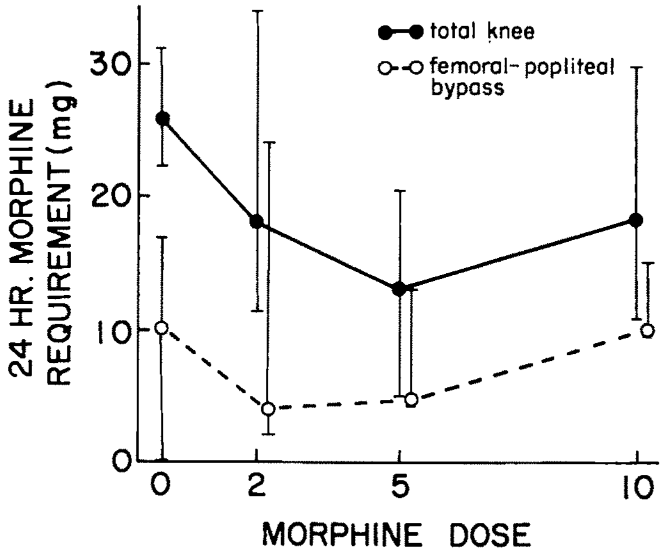

Figure 2. A comparison of 24-hr postoperative parenteral morphine requirements in the two surgical groups with the dose of epidural morphine (median ± quartile). There was a significant relationship with dose in the total knee replacement group ($P < 0.03$) and a significant difference between the two 0-mg control groups ($P < 0.01$).

7.9, 16.6, and 16.2 hr in the total knee replacement group (Fig. 1). There was a significant relationship between epidural morphine dose and the time to first requested pain medication in both surgical groups. There was also a significant difference in the time to first request for medication between the two surgical control groups.

The median cumulative parenteral narcotic (in morphine equivalents), including the epidural dose, administered for the first 24 hours after surgery for the four dosage groups was 13 mg, 4 mg, 5 mg, and 10 mg in the femoral–popliteal bypass group and 26 mg, 18 mg, 13 mg, and 18 mg in the total knee replacement group (Fig. 2). This variable also showed a significant dose relationship for only the total knee replacement group, but again there was a significant difference between the two control surgical groups.

The number of patients requiring no additional analgesic medication for the first 24 hr is seen in Figure 3. There is a significant dose relationship for both groups. More patients in the femoral–popliteal group required no parenteral medication for the first 24 hr at all dose levels.

The 24-hr cumulative time-weighted Visual Analog Scale scores (VAHSR) (Fig. 4) showed a significant dose relationship in both surgical groups. There was no significant difference between the two groups except at the control and 2-mg dose level.

The incidence of nonrespiratory complications is seen in Table 2. There was no relationship between dose and the occurrence of nausea, vomiting, pruritus, or urinary retention in either surgical group. The relationship between the dose of epidural morphine and resting 10-hr postdrug $Pa\text{CO}_2$ (our assessment of respiratory depression) is shown in Figure 5. No elevation of $Pa\text{CO}_2$ levels above those seen in the control group was observed with the 2-mg or 5-mg morphine doses in either surgical group. At a dose of 10 mg of morphine there was a significant increase in the 10-hr resting $Pa\text{CO}_2$ in both surgical groups.

Discussion

The two groups of patients in this study were chosen because of the uniformity of the surgical procedures and the fact that our previous qualitative clinical experience suggested that they had very different degrees of postoperative pain during the 24 hr after surgery. This impression was supported by the observation in control patients that after knee replacement the onset of perioperative pain occurred earlier, the 24-hr parenteral narcotic requirements were greater, and the VASHR was higher than it was after femoral–popliteal bypass.

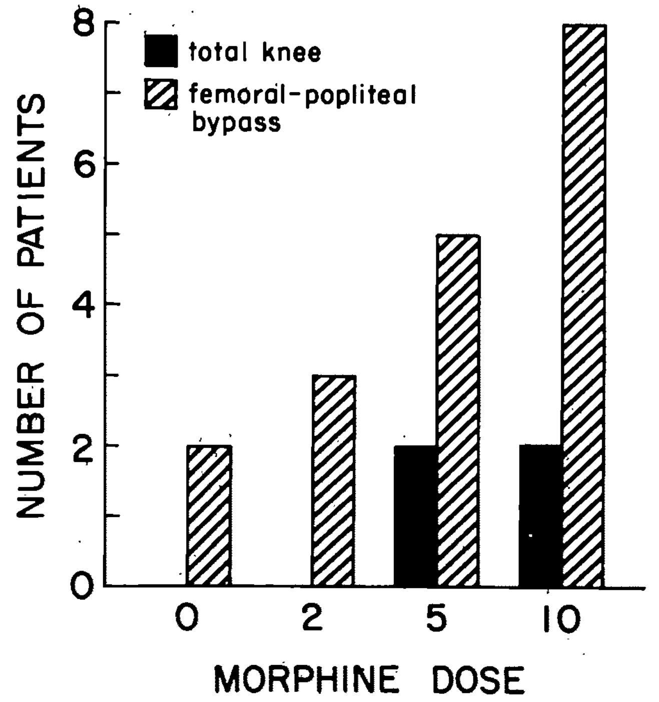

Figure 3. A comparison of the number of patients who requested no additional parenteral narcotic for 24 hr and dose in the two surgical groups. There is a significant relationship with dose in both groups ($P < 0.04$).

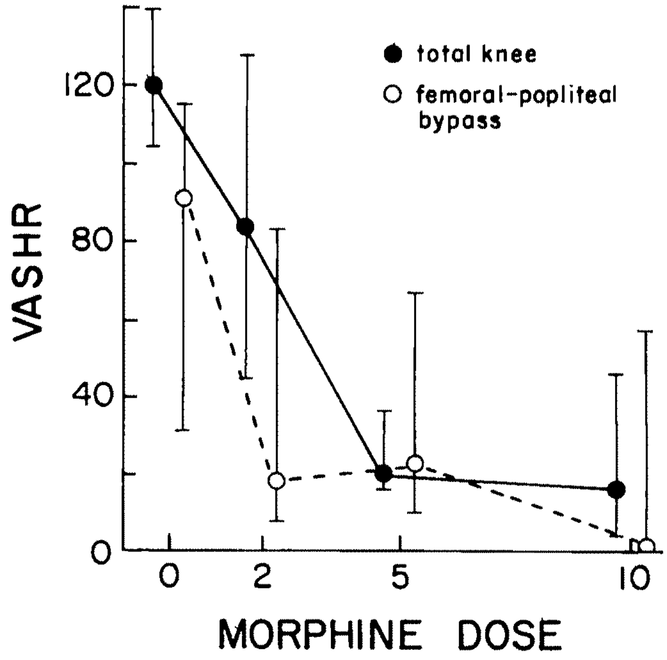

Figure 4. A comparison between dose of epidural morphine and 24-hr time weighted Visual Analog Scale pain scores (median ± quartile). There is a significant relationship for dose in both groups ($P < 0.01$) and a significant difference in the 0-mg and 2-mg dose between surgical groups ($P < 0.05$).

Our results showed that it is possible to improve postoperative analgesia significantly with 5–10 mg of epidural morphine when compared to parenteral opiates given every 4 hr (control group), confirming other work testing this comparison in dose–response studies (3,4,9).

These data suggest that the intensity of postoperative pain is important in determining the efficacy of opiates administered by both the epidural and parenteral routes. Both the 24-hr opiate requirements and VASHR were lower in the femoral–popliteal control group than the total knee control group indicating that there was a decreased efficacy in the total knee replacement group despite the higher dose of additional parenteral medication. Furthermore, the number of patients requiring supplemental postoperative analgesia was greater for all doses of epidural morphine in the total knee replacement group than in the femoral–popliteal bypass group.

Our data agree with most previous studies (3,4,6) that 2 mg of epidural morphine does not provide adequate postsurgical pain relief. However, some studies have found that 2 mg was adequate (5,9). This can be explained either by a lesser pain stimulus than was seen here or a greater pain tolerance for equally perceived pain in their patient groups.

The 10-mg dose provided the most efficacious pain relief in both patient groups. Patients evidenced a significantly lower VASHR, and more patients required no supplemental parenteral narcotic analgesia. The 5-mg dose was also effective in decreasing the VASHR and increasing the time to first requested dose of analgesia in both surgical groups. We cannot determine from our data whether the 10-mg dose was more effective than the 5-mg dose due to an increased duration or to improved receptor occupancy. Because most patients reported no pain for several hours in both groups, it seems probable that the higher dose produced a longer lasting therapeutic level, supporting the first supposition. The observation that the median and quartile range of resting 10-hr Pa_{CO_2} values (Fig. 5) are not altered from normal in the 5-mg group but are significantly increased in the 10-mg dose group at both levels of stimulus suggests that the 5-mg dose is safer in clinical practice. These data agree with two other studies that measured dose–response curves (3,9). These studies showed that 5 mg or 4 mg epidural morphine were sufficient to significantly lower postoperative pain after hysterectomy or cesarean section, whereas the benefits derived from 8 or 10 mg were offset by a higher incidence of postoperative complications.

The most worrisome concern when using epidural opiates for postoperative analgesia is profound res-

Table 2. Incidence of Complications Associated with Epidural Morphine in the Combined Study Population, Femoral–Popliteal Bypass and Total Knee Replacement

	0 mg	2 mg	5 mg	10 mg
Nausea	3	5	2	3
Vomiting	3	3	2	2
Pruritus	4	1	3	3
Urinary retention*	0	0	1	0
Severe respiratory depression	0	0	0	0

*Urinary retention figures are for the total knee replacement group only.

piratory depression. In our patients we did not observe the profound respiratory depression that has been reported by others (3,9,13,14). The 10-hr resting PaCO$_2$ increased significantly in patients receiving the 10-mg dose in both surgical groups. Four patients had a PaCO$_2$ above 50 mm Hg, but none exceeded 54 mm Hg. Profound respiratory depression requiring naloxone reversal has been observed by others after doses of 8 and 10 mg of epidural morphine (3,9,14), and there has been one reported case of profound respiratory depression after 5 mg of epidural morphine (3). The latter case is not in agreement with our findings, which showed that subjects given a 5-mg dose had both normal respiratory rates and normal PaCO$_2$ 10 hr after administration.

Other reported side effects of epidural morphine are urinary retention, nausea, vomiting, and pruritus. Only one patient in the 5-mg knee replacement group required bladder catheterization, a lower incidence of urinary retention than reported in normal volunteers using 10 mg (11,15). We also found a low incidence of both pruritus and nausea and vomiting, neither of which was dose related or different from the incidence in the control patients who received only parenteral opiates. Our incidence is lower than reported in volunteers (16), and in patients having hysterectomy (3) or cesarean sections (5). The latter two studies also found a dose relationship for these complications. The overall reported incidence of nausea, vomiting, and pruritus after epidural opiate administration varies, and our data do fall within the reported range (4,6,7,8,9).

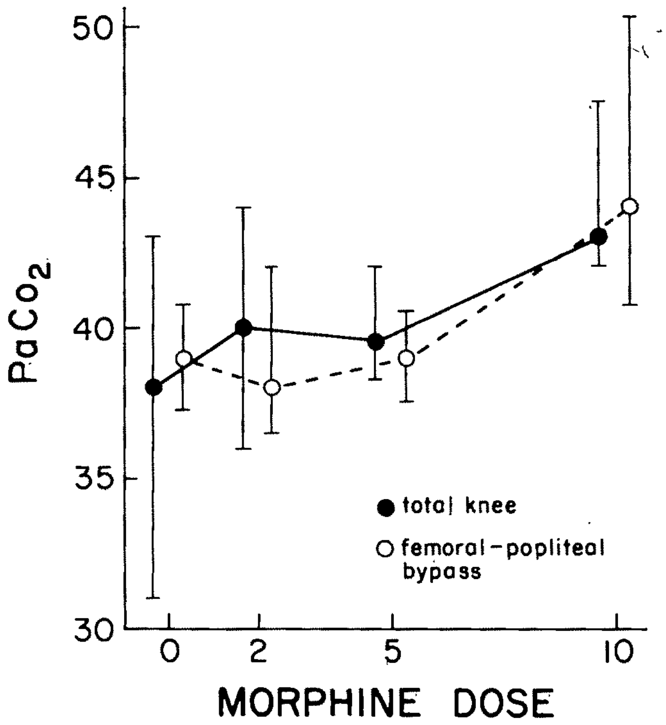

Figure 5. A comparison of PaCO$_2$ 10 hr after administration and dose. There was no relationship between dose and PaCO$_2$ in either surgical group. The 10-mg dose in both surgical groups showed a significant rise in PaCO$_2$ (median ± quartile).

In summary, the present data show that highly effective postoperative analgesia can be provided for patients in the first 16–24 hr after surgery when a 5- or 10-mg dose of epidural morphine in 10 ml saline is injected into the lumbar epidural space prior to wearing off of local epidural anesthesia block. Whereas all doses of epidural morphine yielded better analgesia than parenteral opiates alone, the effectiveness of epidural opiates is both dose related and related to the intensity of the pain stimulus. Because the difference in analgesic efficacy between the 5- and 10-mg dose is small and the incidence of mild late respiratory depression is significantly higher when the 10-mg dose is used, we recommend 5 mg epidural morphine for clinical practice when morphine is the drug chosen for spinal opoid analgesia.

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Failure of the Platelet-Halothane Nucleotide Depletion Test as a Diagnostic or Screening Test for Malignant Hyperthermia

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BRITT BA, SCOTT EA. Failure of the platelet-halothane nucleotide depletion test as a diagnostic or screening test for malignant hyperthermia. Anesth Analg 1986;65:171–5.

A platelet-halothane nucleotide or bioassay test has been suggested as an accurate means for diagnosis of malignant hyperthermia (MH). For the last three years we performed this test in all patients at risk for MH and in all normal control patients undergoing skeletal muscle biopsy in our diagnostic unit. The reliability of the platelet-halothane nucleotide test has been assessed on the basis of the presence or absence of a previous MH reaction and degree of relationship of relatives to those who have had reactions, and on the basis of caffeine-halothane contracture test values (positive or negative for MH). We have found no significant difference in platelet-halothane nucleotide test values in malignant hyperthermia susceptible (MHS) patients or relatives of MHS patients and normal controls, and no relationship between the nucleotide test and caffeine-halothane contracture test results. We conclude that the platelet-halothane nucleotide test is not of assistance in the diagnosis of or in the screening for MH.

Key Words: HYPERTHERMIA, MALIGNANT.

The diagnosis of malignant hyperthermia (MH) requires a large muscle biopsy to provide samples for the caffeine-halothane contracture test (1,2), which is presently the most reliable method of identifying malignant hyperthermia susceptible (MHS) persons. Because it is highly invasive, expensive, and time consuming, this procedure can be applied to only a small portion of those at risk for malignant hyperthermia. A reliable, inexpensive, and noninvasive test is therefore urgently needed to enable identification of all those at risk within known or suspected MHS families and to enable determination of the incidence of MHS in the general population. Because MH is now thought to be a widespread membrane defect (3), selection of tissue for measurement more accessible and expendable than muscle seems appropriate.

Recently, Solomons et al. have published two articles describing such a test utilizing platelets (4,5). The authors chose platelets because they possess calcium storage vesicles (6–11) and contractile elements (12,13) similar to those of skeletal muscle. The procedure is based on the observation that in human platelets halothane accelerates the conversion of high energy nucleotides (ATP and ADP) to low energy nucleotides (hypoxanthine, xanthine, and AMP). This conversion of high to low energy nucleotides by halothane is said to be greater in MHS patients than in normal control subjects. The results of this are expressed in the form of a double ratio (defined later in this paper).

We have been anxious to have in our armamentarium a noninvasive screening test in order to minimize the number of invasive skeletal muscle biopsies we are presently performing on MHS patients. We therefore added the platelet-halothane nucleotide depletion test to our muscle biopsy investigations. We have tried to ensure that our method was as close as possible to that of Solomons and Masson (4).

Methods

All patients had both a caffeine-halothane contracture test and a platelet-halothane nucleotide depletion test performed.

Technique for Measurement of Platelet Nucleotides

Platelet nucleotides were measured by the method of Solomons and Masson (4). The skin was wiped with isopropyl alcohol that was then allowed to evaporate.

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A tourniquet was lightly applied. Two ml of blood was drawn from each patient and discarded. Ten ml of blood was then drawn into a Vacutainer through a #20 needle. Each tube was gently inverted several times. The stoppers were then removed. When difficulty with venupuncture was encountered, the sample was discarded. No refrigeration was employed. Each tube was spun in a table top centrifuge with a bucket type head at 800 rpm for 18 min. If the platelet rich plasma (PRP) was contaminated with erythrocytes the sample was recentrifuged. Then all except the last half ml of the PRP was transferred via a plastic Eppendorf pipette tip mounted in a Gibson pipette into 5-ml Falcon high molecular weight polypropylene tubes (75 × 10 mm). The tubes containing PRP were capped and gently inverted twice. PRP, 0.4 cc, was pipetted into another set of Falcon polypropylene tubes (numbers 1, 2, and 3). To each of these tubes 0.0, 2.0, and 4.0 μl, respectively, of undissolved liquid halothane was added by means of a Hamilton syringe. The tip of this syringe was placed under the surface of each PRP containing tube but was not allowed to touch the bottom of the tube. The tubes were then immediately tightly capped, mixed by gentle swirling, incubated in a water bath at 37°C for 15 min, and spun with their caps on to prevent evaporation of halothane at 2500 rpm in a table top centrifuge for 2 min. The supernatants were discarded leaving a platelet pellet. Pellets contaminated with erythrocytes were discarded. The tubes were placed on ice, after which 0.1 ml of clear, cold 0.4M perchloric acid was immediately added to each tube. The tubes were shaken vigorously with a Vortex mixer at maximum speed to break up the platelets and release the nucleotides and then were allowed to stand for 5–10 min on ice. After respinning at 2500 rpm in a table top centrifuge for 3 min the tubes were cooled on ice. The supernatants (nucleotides dissolved in perchloric acid) were decanted into micro test tubes and placed on ice and kept there until analysis the same day. Supernatants showing evidence of turbidity were discarded. The platelet nucleotides were measured isocratically in a Waters high pressure liquid chromatograph (HPLC). This was done by first injecting 10 μl of nucleotide–perchloric acid mixture into a Waters μ-Bondapak C18 column and then pumping 0.1M KH_2PO_4 through the column at 2 ml/min. The peaks were detected at 254 nm. The concentration of each nucleotide was derived from peak heights. The nucleotide ratio was calculated as the following:

$$\frac{\text{ATP} + \text{ADP}}{\text{xanthine} + \text{hypoxanthine} + \text{AMP}} \qquad (1)$$

The halothane ratio was calculated as the following:

$$\left(1 - \frac{\begin{array}{c}\text{nucleotide ratio (R)}\\ \text{in the presence of halothane}\end{array}}{\begin{array}{c}\text{nucleotide ratio (R)}\\ \text{in the absence of halothane}\end{array}}\right) \times 100 \qquad (2)$$

We also calculated an ATP ratio:

$$\left(1 - \frac{\text{ATP in the presence of halothane}}{\text{ATP in the absence of halothane}}\right) \times 100 \quad (3)$$

according to the method of Giger and Kaplan (12).

Caffeine-Halothane Contracture Test (CHC)

The CHC test was performed by the method previously described by us (1,2). The mM of caffeine required to increase the resting tension of isolated skeletal muscle fascicles by 1 g in the absence of halothane was termed the caffeine specific concentration (CSC). The mM of caffeine required to increase the resting tension of isolated skeletal muscle fascicles by 1 g in the presence of 1.0 vol% halothane was termed the caffeine specific concentration-halothane (CSC-H).

Classification by Degree of Relationship to MHS Patients

Patients were also classified and analyzed according to closeness of relationship of individuals who had had MH reactions as follows:

0, MHS patients who had had one or more previous reactions characterized by fever, rigidity, tachycardia, and metabolic acidosis.

1, First degree relatives of an MHS patient, i.e., sibling, parent or offspring.

2, Second degree relatives of an MHS patient, i.e., niece, nephew, aunt, uncle, grandparent, or grandchild.

3, Third degree relatives of an MHS patient, i.e., first cousin, grand niece, grand nephew, great aunt, great uncle, great grandparent, or great grandchild.

4, Fourth degree relatives of an MHS patient, i.e., second cousins.

5, Fifth degree relatives of an MHS patient, i.e., third cousins, etc. to tenth degree relatives.

Classification of Caffeine-Halothane Contracture Test Values

For a patient in our laboratory to be considered positive for MH one or more of the following had to be

Table 1. Platelet Nucleotide Ratios: Normal Controls vs MHS Patients and MHS and Normal Relatives

	MHS patients[a]	First degree relatives[b]	Second degree relatives[c]	Third degree relatives[d]	Fourth degree relatives[e]	Fifth–tenth degree relatives[f]	Control
n (sample size)	58	88	33	18	16	19	23
Mean[g]	54.26	57.09	52.58	52.44	49.88	58.16	53.57
SEM	1.77	1.62	1.78	4.23	3.77	3.32	3.07
Student's *t*-test[h]	0.20	1.00	−0.30	−0.22	−0.76	1.01	

[a] MHS patients who had had one or more previous reactions characterized by fever, rigidity, tachycardia, and metabolic acidosis.
[b] Sibling, parent, or offspring.
[c] Niece, nephew, aunt, uncle, grandparent, or grandchild.
[d] First cousin, grand niece, grand nephew, great aunt, great uncle, great grandparent, or great grandchild.
[e] Second cousins (other types of relatives were either dead or not yet born).
[f] Third cousins, etc., to tenth degree relatives.
[g] Mean, mean arithmetic nucleotide ratio. [h] Student's *t*-test was not significant ($P > 0.05$).

Table 2. Platelet Nucleotide Ratios: Normal Controls vs MHS Patients and MHS Relatives with Various Combinations of Caffeine–Halothane Contracture Tests Positive for Malignant Hyperthermia

	H (all patients +ve with halothane)	C (all patients +ve with caffeine)	H+C (all +ve patients except type K)	H+C+K (All +ve patients)	Control
n (sample size)	28	84	88	172	23
Mean arithmetic nucleotide ratio	60.21	53.69	54.03	55.07	53.57
SEM	2.68	1.69	1.63	1.11	3.07
Student's *t*-test	1.64 (ns)	0.03 (ns)	0.13 (ns)	0.47 (ns)	

Abbreviations: H, patients with contractures in the presence of halothane alone; C, lower than normal CSC (mild MH); K, patients with lower than normal CSC-Hs, i.e., patients with greater than normal responses only in the combined presence of caffeine plus halothane (the most mild variant of MH); +ve with halothane, contracture of a muscle fascicle in the presence of halothane alone; +ve with caffeine, lower than normal CSC; ns, not significant.

present: 1) A contracture of at least 0.1 g in the presence of halothane alone (normal control muscle exhibited no elevation of resting tension in the presence of halothane alone); 2) a CSC of equal to or less than 4.1 mM of caffeine; 3) a CSC-H of less than 1.2 mM of caffeine.

MHS relatives were those persons whose CHC tests met the above criteria, who had not themselves had MH reactions, but who had one or more relatives who had had at least one MH reaction. Normal relatives were those persons whose CHC test results did not meet the above criteria, who had not themselves had MH reactions, but who had one or more relatives who had had at least one MH reaction. Controls were those individuals who had had CHC tests performed but who had no history of MH reactions in themselves or in their relatives.

Classification of Various Combinations of Caffeine-Halothane Contracture Test Values

MH investigators have not yet been able to achieve uniformity of performance and interpretation of the caffeine-halothane contracture test (1,14–25, H. Ording, R. Reynolds, personal communications). This may well be because the subjects being tested comprise more than one phenotype, or because of inadvertent and unnoticed differences in the concentration of halothane in the bathing chamber. A few investigators believe that only halothane is a useful test agent (25, H. Ording, personal communication). A few others use both halothane and caffeine on separate strips of muscle but state that halothane provides more valid results (16–18). The majority consider that a greater than normal response to either halothane alone or caffeine alone constitutes evidence for MH, that patients who develop contractures in the presence of halothane alone nearly always have a lower than normal threshold for caffeine-induced contractures, but that those with lower than normal thresholds for caffeine-induced contractures do not always exhibit halothane-induced contractures (1,19–22,24, R. Reynolds, personal communication). A few of these investigators also recognize that simultaneous application of both halothane and caffeine to the muscle is necessary to ensure identification of all mild cases (1,19,21,22,24). Thus some very mildly afflicted MHS individuals appear to these workers to react normally with either halothane or with caffeine alone but to develop greater than normal responses in the combined presence of caffeine and halothane, i.e., to have

Table 3. Platelet ATP Depletion: Normal Controls vs MHS Patients and MHS and Normal Relatives

	MHS patients[a]	First degree relatives[a]	Second degree relatives[a]	Third degree relatives[a]	Fourth degree relatives[a]	Fifth–tenth degree relatives[a]	Control
n (sample size)	58	88	33	18	16	19	23
Mean[b]	46.90	47.85	45.00	39.44	47.88	48.37	45.91
SEM	2.22	2.12	1.76	3.72	4.60	3.72	3.67
Student's *t*-test[c]	0.23	0.43	−0.25	−1.22	0.34	0.47	

[a] See Table 1 footnotes for definitions.

[b] Mean, mean arithmetic ATP depletion.

[c] Student's *t*-test was not significant ($P > 0.05$).

Table 4. Platelet ATP Depletion: Normal Controls vs MHS Patients and MHS Relatives with Various Combinations of Caffeine–Halothane Contracture, Tests Positive for Malignant Hyperthermia

	H (patients +ve with halothane)	C (patients +ve with caffeine)	K (patients +ve only with caffeine + halothane)	H+C (all +ve patients except type K)	H+C+K (all +ve patients including type K)	Control
n (sample size)	28	84	84	88	172	23
Mean arithmetic ATP depletion	47.32	44.19	48.26	44.64	46.41	45.91
SEM	3.52	1.81	1.94	1.74	1.31	3.67
Student's *t*-test	0.28 (ns)	−0.44 (ns)	0.56 (ns)	−0.33 (ns)	0.13 (ns)	

Abbreviations: H, patients with contractures in the presence of halothane alone; C, lower than normal CSC (mild MH); K, patients with lower than normal CSC-Hs, i.e., patients with greater than normal responses only in the combined presence of caffeine plus halothane (the most mild variant of MH); +ve with halothane, contracture of a muscle fascicle in the presence of halothane alone; +ve with caffeine, lower than normal CSC; ns, not significant.

lower than normal thresholds for caffeine induced contractures in the presence of halothane.

The patients, therefore, were classified as follows:

1. C, lower than normal CSC (mild MH).
2. K, patients with lower than normal CSC-Hs, i.e. patients with greater than normal responses only in the combined presence of caffeine plus halothane (the most mild variant of MH).
3. H, patients with contractures in the presence of halothane alone.
4. H + C, all those with muscle biopsies positive for MH excluding type K.
5. H + C + K, all those with muscle biopsies positive for MH including type K.

Results

The results for nucleotide depletion ratios are shown in Tables 1 and 2 and for ATP depletion ratios in Tables 3 and 4.

Halothane consistently lowered ATP and ADP levels and increased xanthine, hypoxanthine, and AMP levels. Thus all percent depletions were less than 100—often much less so. In spite of the consistency of the above changes, all mean nucleotide ratios, including those of MHS patients and those of individuals with type H muscle biopsies, were less than 60%—the value given by Solomons and Masson as being the percent reduction of the nucleotide ratio below which an individual is judged to be at an insignificant risk for MH (4). In fact, the nucleotide ratio values were actually lower in the second to fourth degree MHS relatives than in normal controls (Table 1).

Differences in the nucleotide ratios between normal controls and MHS patients or MHS first to tenth degree relatives, or between normal controls and individuals with positive caffeine-halothane contracture tests were, in all cases, not statistically significant. The results for the ATP ratio were also not significant. Thus percent depletions were often lower in MHS patients and relatives and in those with biopsies positive for MH than they were in normal controls (Tables 3 and 4). This is the converse of the results obtained by Solomons (4). Again, all comparisons with normal controls were statistically insignificant.

Discussion

Our study does not elucidate the reason for the decrease in the high energy nucleotides and the increase in the low energy nucleotides induced in platelets by halothane. However, the reduction in ATP and the increase in cAMP may be due to stimulation of adenylate cyclase by halothane, an action already demonstrated by Walter et al (26).

Our results are in essential agreement with those of Giger and Kaplan (12) on ATP ratios and with those of Verburg et al. on ATP ratios (27), but not with those of Solomons et al. (4,5). Unlike Solomons et al., we found no statistical difference in platelet nucleotide values between normal and MHS patients and no relationship between caffeine-halothane contracture tests and platelet nucleotide values.

In conclusion, measurement of the nucleotide ratio or the ATP ratio in platelets is not a useful test in the diagnosis or screening of MHS patients.

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Absence of Interaction of Cimetidine and Ranitidine with Intravenous and Oral Midazolam

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GREENBLATT DJ, LOCNISKAR A, SCAVONE JM, BLYDEN GT, OCHS HR, HARMATZ JS, SHADER RI. Absence of interaction of cimetidine and ranitidine with intravenous and oral midazolam. Anesth Analg 1986;65:176–80.

Eight healthy volunteers received a single 5-mg intravenous dose of the imidazobenzodiazepine derivative midazolam on three occasions in random sequence: a, control, with no other treatment; b, during coadministration of cimetidine, 300 mg every 6 hr; c, during coadministration of ranitidine, 150 mg every 12 hr. Midazolam kinetics in each trial were determined from multiple plasma midazolam levels measured by gas chromatography for 24 hr after each dose. High pressure liquid chromatography analysis of plasma also verified compliance with cimetidine (mean level, 0.61 μg/ml) and ranitidine (mean level, 0.36 μg/ml) regimens. Analysis of variance indicated no significant differences in mean values for trials a, b, and c in midazolam elimination half-life (2.25 vs 2.02 vs 2.05 hr), volume of distribution (2.13 vs 2.14 vs 2.16 L/kg) or total clearance (10.8 vs 12.2 vs 12.3 ml·min^{-1}·kg^{-1}). In a second study, six subjects received a 15-mg oral dose of midazolam on three occasions identical to those described above. Again, there were no significant differences among trials a, b, and c in midazolam peak plasma level (90 vs 95 vs 117 ng/ml), time of peak level (0.65 vs 1.45 vs 0.90 hr after dose), elimination half-life (3.04 vs 3.38 vs 3.30 hr), or apparent oral clearance (16.2 vs 14.3 vs 13.8 ml·min^{-1}·kg^{-1}) Thus the usual therapeutic doses of cimetidine or ranitidine do not significantly alter the kinetics of intravenous or oral midazolam in healthy individuals.

Key Words: GASTROINTESTINAL TRACT, HISTAMINE-ANTAGONISTS. HYPNOTICS, BENZODIAZEPINES—midazolam. INTERACTIONS (DRUG), HISTAMINE-ANTAGONISTS—midazolam.

Midazolam is an imidazobenzodiazepine derivative currently under evaluation as a parenterally administered premedicant and induction agent, as well as an orally administered hypnotic agent (1–4). The major metabolic pathway of midazolam in humans involves hepatic microsomal oxidation, leading to at least two hydroxylated metabolites that are subsequently conjugated and excreted in the urine (5). Midazolam is characterized pharmacokinetically by a large volume of distribution, a high value of hepatic clearance, and a short elimination half-life (1–4,6).

H-2 receptor antagonists such as cimetidine and ranitidine are commonly administered in the perioperative period to prevent harmful complications of aspiration of acidic gastric contents, or to prevent stress ulceration in the postoperative period (7). H-2 antagonists also are widely prescribed for a variety of other indications to hospitalized and ambulatory patients who may be taking these medications at the time they reach surgery. For this reason the possible pharmacokinetic interaction of H-2 antagonists with midazolam is of potential clinical importance. Cimetidine has the well-established property of impairing hepatic microsomal oxidation of drugs, leading to reduced clearance of other medications metabolized by that pathway when coadministered with cimetidine (8,9). Ranitidine, on the other hand, appears to lack this microsomal inhibiting property and has been implicated in fewer drug interactions of this type (10). The present study evaluated the pharmacokinetic interaction of midazolam, administered both intravenously and orally, with the H-2 antagonists cimetidine and ranitidine.

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Table 1. Plasma Cimetidine and Ranitidine Concentrations Measured during the Intravenous Midazolam Interaction Study

	Mean (±SEM) plasma concentration (μg/ml)	
	Cimetidine	Ranitidine
Time after midazolam administration		
Before	.85 ± 0.20	.47 ± 0.11
4 hr	.58 ± 0.13	.36 ± 0.07
8 hr	.59 ± 0.08	.24 ± 0.10
12 hr	.56 ± 0.05	.39 ± 0.07
24 hr	.45 ± 0.20	.35 ± 0.07

Methods

The study protocols were reviewed and approved by the Human Investigation Review Committee at New England Medical Center Hospital. All subjects gave written informed consent prior to participation.

Intravenous Midazolam Study

Eight healthy volunteers, aged 22–46 yr, participated. Five were male and three were female. All were healthy, active, ambulatory adults with no evidence of medical disease and receiving no other medications.

Subjects participated in a single-dose, three-way crossover study. On each occasion they received a single 5-mg intravenous dose of midazolam by 1-min intravenous infusion. The three modes of administration were as follows: Midazolam administered alone, without concurrent medications (control); midazolam given intravenously during coadministration of cimetidine, 300 mg 4 times daily, beginning 24 hr before and continuing for 24 hr after midazolam administration; and midazolam given intravenously during coadministration of ranitidine, 150 mg every 12 hr, beginning 24 hr before and continuing for 24 hr after midazolam administration. At least one week elapsed between trials, the sequence of which was randomized.

For each midazolam administration trial, subjects received a single 5-mg dose of midazolam base (in the form of the hydrochloride salt) by intravenous infusion into an antecubital vein over a period of 1 min. Venous blood samples were drawn through an indwelling cannula (kept patent by slow infusion of physiologic saline), or by venipuncture, into heparinized Vacutainer tubes. Samples were taken before midazolam dosage, just at the end of the infusion, and again 5, 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 18 and 24 hr later. Blood samples were centrifuged and the plasma separated and frozen until the time of assay.

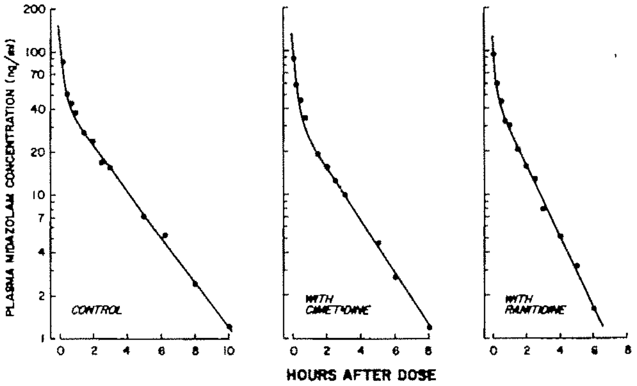

Figure 1. Plasma midazolam concentrations in a representative volunteer after a single 5-mg intravenous dose of midazolam in each of the three treatment conditions.

Oral Midazolam Study

Six healthy male volunteers (different from the subjects who took part in the intravenous midazolam study) participated. All were healthy, active, ambulatory adults with no evidence of medical disease and receiving no other medications.

Subjects participated in a single-dose, three-way crossover trial. The three modes of administration (control, with cimetidine, and with ranitidine) were identical to those described above for the intravenous midazolam study. At least 1 week elapsed between trials, the sequence of which was randomized.

Subjects fasted for 8 hr before and for 3 hr after each midazolam administration. The 15-mg oral tablet of midazolam base (in the form of the hydrochloride salt) was administered with 100–200 ml of tap water. Venous blood samples were drawn as described for the intravenous study before the dose and 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 18 and 24 hr later. Venous blood samples were centrifuged, and the plasma separated and frozen until the time of assay.

Analysis

Concentrations of midazolam in all plasma samples were determined by electron-capture gas-liquid chromatography, details of which are described previously (11,12). The sensitivity limit is approximately 1 ng of midazolam per ml of plasma. All samples from a given subject's set of three trials were extracted and analyzed together on the same day using the same calibration standards.

In the intravenous midazolam study, compliance with the prescribed cimetidine or ranitidine coadministration regimens was verified by measurement of cimetidine or ranitidine plasma concentrations, as ap-

Table 2. Kinetic Variables for Intravenous and Oral Midazolam

	Mean (±SEM) value			Value of F[a] from ANOVA
	Control	With cimetidine	With ranitidine	
Intravenous midazolam, 5 mg (n = 8)				
Distribution half-life (hr)	0.30 ± 0.04	0.25 ± 0.02	0.27 ± 0.05	0.57 (NS)[b]
Elimination half-life (hr)	2.25 ± 0.20	2.02 ± 0.19	2.05 ± 0.14	1.24 (NS)
V_1 (L/kg)	0.71 ± 0.11	0.66 ± 0.04	0.72 ± 0.10	0.36 (NS)
Vd (L/kg)	2.13 ± 0.34	2.14 ± 0.26	2.16 ± 0.34	0.01 (NS)
Clearance (ml·min^{-1}·kg^{-1})	10.8 ± 1.4	12.1 ± 0.92	12.3 ± 1.8	1.50 (NS)
Oral midazolam, 15 mg (n = 6)				
Peak plasma concentration (ng/ml)	90 ± 27	95 ± 30	117 ± 32	2.17 (NS)
Time of peak (hr after dose)	0.65 ± 0.10	1.45 ± 0.66	0.90 ± 0.40	0.78 (NS)
Elimination half-life (hours)	3.04 ± 0.50	3.37 ± 0.54	3.30 ± 0.67	1.43 (NS)
Total AUC (ng/ml × hr)	297 ± 114	267 ± 45	332 ± 110	0.52 (NS)
Apparent oral clearance (ml·min^{-1}·kg^{-1})	16.2 ± 4.4	14.3 ± 3.0	13.8 ± 2.8	1.07 (NS)

[a] Degrees of freedom: 2,14 for intravenous study; 2,10 for oral study.
[b] NS, not significant.

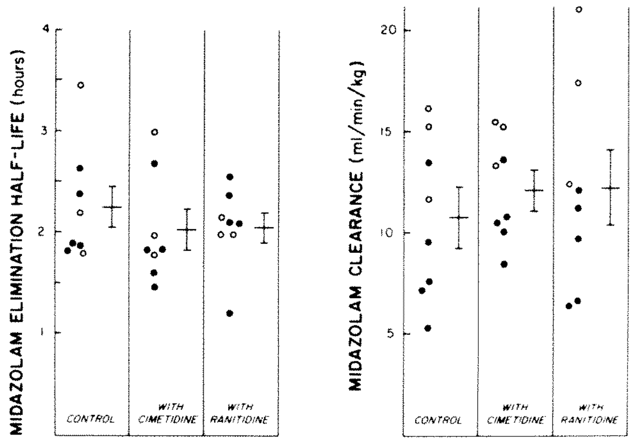

Figure 2. Individual and mean (±SEM) values of midazolam elimination half-life (left) and total clearance (right) in the intravenous midazolam study. Closed circles indicate men; open circles indicate women. See Table 2 for statistical analysis.

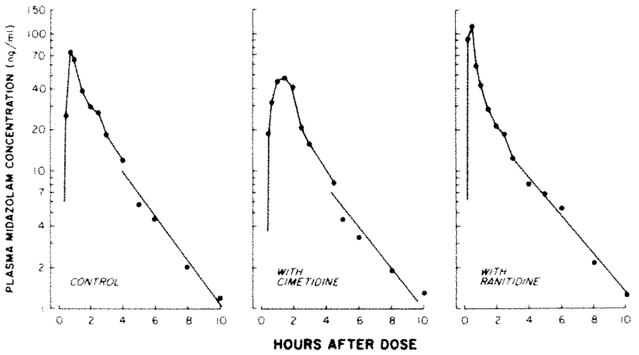

Figure 3. Plasma midazolam concentrations in a representative volunteer after a single 15-mg oral dose of midazolam in each of the three treatment conditions.

propriate, by HPLC (13) in samples drawn before midazolam administration and 4, 8, 12, and 24 hr after midazolam dosage.

Kinetic and Statistical Analysis

Plasma midazolam concentrations after intravenous infusion of midazolam were analyzed by iterative nonlinear least-squares regression technique. Data points were fitted to a linear sum of two or three exponential terms (14,15). Exponents and infusion-corrected coefficients from the function of best fit were used to calculate the following kinetic variables: central compartment volume (V_1), total apparent volume of distribution using the area method (Vd), initial distribution half-life, apparent elimination half-life, and total clearance. After oral midazolam administration, the apparent elimination half-life was calculated using the slope (β) of the terminal log-linear phase of the plasma concentration curve. Area under the curve until the final data point was determined using the trapezoidal method, and extrapolated to infinity by addition of the final concentration divided by beta. This yielded the total area under the curve (AUC). Apparent oral clearance was calculated as the administered dose (15 mg) divided by AUC. Also evaluated were peak plasma midazolam concentrations and the times of peak concentration.

Analysis of variance for repeated measures was used to determine overall differences between treatment conditions in each kinetic variable.

Results

Plasma cimetidine and ranitidine concentrations indicated good compliance with the prescribed regimen (Table 1). Concentrations of these drugs were con-

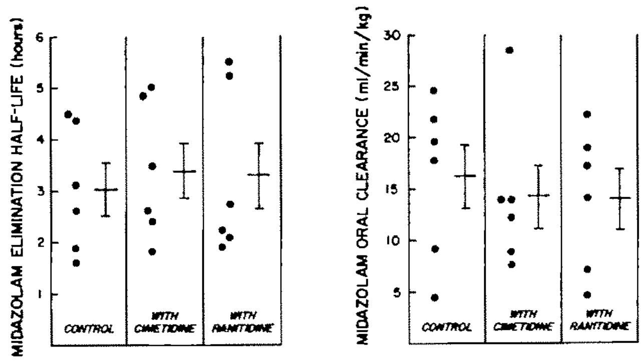

Figure 4. Individual and mean (±SEM) values of midazolam elimination half-life (left) and apparent oral clearance (right) in the oral midazolam study. See Table 2 for statistical analysis.

sistent with those attained during usual clinical use of therapeutic doses (16,17).

Figure 1 shows representative plasma midazolam concentration curves after intravenous administration of midazolam. Although both male and female subjects participated in the study, the sample sizes (5 male and 3 female) were not large enough to allow meaningful statistical analysis with stratification for gender. Therefore data from all eight subjects were analyzed together. There were no significant differences between the three treatment conditions in any of the kinetic variables for midazolam (Table 2, Fig. 2). Values of midazolam elimination half-life in the control, cimetidine, and ranitidine treatment conditions were 2.25, 2.02, and 2.05 hr, respectively. Corresponding values for total clearance of midazolam were 10.8, 12.2, and 12.3 $\mathrm{ml{\cdot}min^{-1}{\cdot}kg^{-1}}$, respectively. These values are consistent with those reported in previous kinetic studies of midazolam in healthy young volunteers (1–6).

Figure 3 shows representative plasma midazolam concentration curves in the oral midazolam study. Again there were no significant differences between treatment conditions in any of the kinetic variables for midazolam (Table 2, Fig. 4). Values of elimination half-life were 3.0, 3.4, and 3.3 hr, respectively. Corresponding values of oral clearance were 16.2, 14.3, and 14.0 $\mathrm{ml{\cdot}min^{-1}{\cdot}kg^{-1}}$.

Discussion

The present study evaluated the potential pharmacokinetic interaction of the H-2 receptor antagonists cimetidine and ranitidine with the imidazobenzodiazepine agent midazolam, after both intravenous and oral midazolam administration. This and previous studies have demonstrated that the total clearance of midazolam (known to be accomplished principally by hepatic microsomal oxidation) falls in the range of approximately 50% of hepatic blood flow (1–6). Therefore, the clearance of midazolam after intravenous administration should be susceptible to the microsomal enzyme inhibiting properties of cimetidine. Surprisingly, cimetidine was found to have no significant effect on any of the kinetic variables for midazolam. This contrasts with the well-established capacity of cimetidine to impair the clearance of other oxidized benzodiazepines, including chlordiazepoxide (18), diazepam (13,19), desmethyldiazepam (20), desalkylflurazepam (21), alprazolam (22), and triazolam (22). The absence of interaction of cimetidine with midazolam was true despite the documented attainment of therapeutic plasma cimetidine concentrations (16). Thus the inhibition of hepatic drug oxidation by cimetidine appears not to be invariable. In other studies, cimetidine also did not impair the clearance of the oxidized nonsteroidal antiinflammatory agent ibuprofen (23,24).

Unlike cimetidine, ranitidine has a greatly reduced capacity to impair hepatic microsomal oxidation of other medications (10,25). This was verified in the present study documenting that coadministration of ranitidine, with "therapeutic" plasma ranitidine concentrations verified (17), did not alter the pharmacokinetics of intravenous or oral midazolam. This contrasts with a prior reported interaction of ranitidine and oral midazolam (26).

The present study involved relatively small sample sizes, and it is possible that alterations in midazolam kinetics due to cimetidine or ranitidine—particularly after oral midazolam administration—might have attained significance had the sample size been larger. Furthermore, our study was performed on healthy young volunteers and should be further verified in other patient populations, including elderly patients and those with concomitant diseases. Nonetheless, the findings suggest that a clinically important pharmacokinetic interaction of intravenous or oral midazolam with the H-2 antagonists cimetidine or ranitidine is unlikely to occur in clinical practice.

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ANESTH ANALG
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Halothane and Isoflurane Anesthesia in Pediatric Outpatients

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KINGSTON HGG. Halothane and isoflurane anesthesia in pediatric outpatients. Anesth Analg 1986;65:181–4.

Halothane or isoflurane was used to induce anesthesia in children scheduled for outpatient surgical procedures. Both agents were administered at predetermined rates until comparable concentrations in end-expired air were reached. Induction of anesthesia, as well as the time taken before tracheal intubation was possible, was protracted in patients given isoflurane. In the recovery period, the times taken to respond to pharyngeal suction, to tracheal extubation, and to the first cry were similar for both anesthetic agents.

Key Words: ANESTHETICS, VOLATILE—halothane, isoflurane. ANESTHESIA, PEDIATRIC. ANESTHESIA, OUTPATIENT.

Increasing numbers of pediatric minor surgical procedures are being undertaken on an outpatient basis. In such a setting, anesthesiologists prefer anesthetic techniques most likely to be associated with a short recovery period uncomplicated by excessive drowsiness or vomiting. Measures advocated to achieve these goals have included the use of preparatory film shows, different premedication techniques (1,2), or deliberate avoidance of premedication (3), as well as the presence of parents in the induction area and less dependence on pharmacologic agents (4). Inhalation induction of anesthesia remains popular in many centers, and because halothane rapidly and predictably produces loss of consciousness it has continued for nearly three decades as the most popular inhaled agent for use in outpatient general anesthesia in children. Many pediatric patients are unpremedicated (either by preference of the anesthesiologist or due to scheduling difficulties) and may arrive in the operating room anxious or crying. Because these patients have elevated serum catecholamine levels, they could develop cardiac dysrhythmias if halothane were used. Isoflurane may be an attractive alternative to halothane in outpatient surgery because isoflurane is associated with less myocardial sensitization to catecholamines (5), and its low blood gas solubility, when compared with halothane (1.4 vs 2.3) (6), should be associated with more rapid induction of and recovery from anesthesia. However, because increased airway irritability has been reported with the use of isoflurane, controversy exists as to whether isoflurane is clinically acceptable for inhalation induction of anesthesia in children (7,8).

We administered either halothane or isoflurane to unpremedicated pediatric outpatients at a set rate and to a predetermined concentration of halogenated agent in the expired air. We wished to evaluate whether isoflurane is associated with equally rapid induction of anesthesia when compared with halothane administered at a similar rate, and whether recovery from anesthesia is more rapid with halothane or isoflurane.

Methods

Forty unpremedicated children between the ages of 1 and 6 yr classified as ASA I were studied. The study was approved by the ethics committee of our hospital. These children were scheduled for either orthopedic, ear, nose, and throat (ENT), general surgical, or urological procedures. The patients were randomly divided into two groups, *A* and *B*, *A* ($n = 20$) to receive halothane and *B* ($n = 20$) isoflurane. On entering the operating room ECG leads, a blood pressure cuff, and a wrist doppler were attached. In each case the anesthetic was managed by one individual while recording was done by an independent observer. Because it was possible to detect the odor of the anesthetic agent used during the induction technique, no attempt was made to withhold the choice of anesthetic agent from the observer. After baseline measurements of blood pressure and pulse rate, induction of anesthesia commenced using 70% nitrous oxide in oxygen and a cherry-scented mask. After 1 min the halogenated agent was introduced (in each instance

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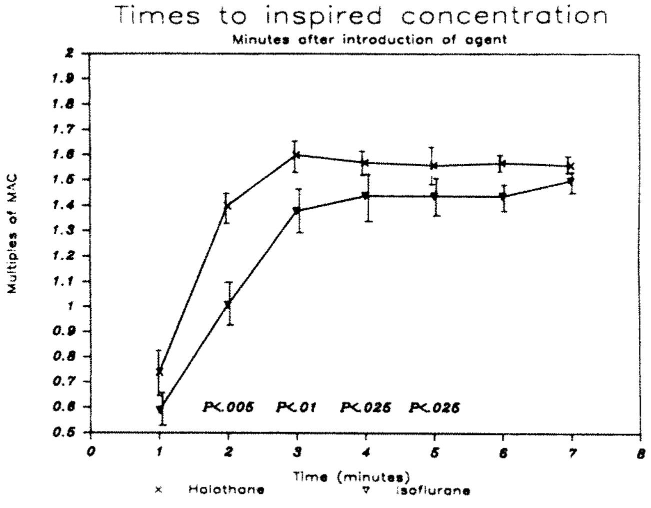

Figure 1. Halothane achieved comparable MAC values more rapidly than isoflurane in expired gas during induction of anesthesia. Values are expressed as multiples of MAC ± SEM.

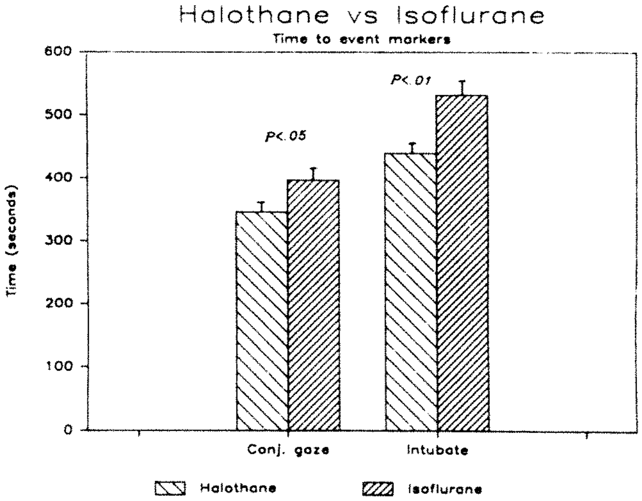

Figure 2. Conjugate gaze and intubation of the trachea occurred more rapidly with halothane than with isoflurane. Each histogram represents time (secs) ± SEM.

using the same calibrated isoflurane and halothane vaporizers) starting with 0.25% and increasing by 0.25% each 6 breaths. A nonrebreathing, valved delivery system was used that allowed analysis of the agent by using a precalibrated piezoelectric quartz crystal (9).

Each anesthetic was administered to the same end-point concentration in the end-expired air. For comparison the measured expired concentration of each agent was converted to the MAC value (in this instance the MAC of halothane was considered as 0.75% and isoflurane as 1.15%) (10). If coughing or breath holding occurred, the concentration of the inspired agent was decreased by 0.5% and, once the coughing ceased, was again increased according to the protocol. Once 1.5 MAC of the agent was attained in the expired air, this concentration was maintained with oxygen and nitrous oxide until the end of the surgical procedure. The MAC of the anesthetic received by the patient therefore included 1.5 contributed by the halogenated agent and 0.7 by nitrous oxide. During induction of anesthesia, blood pressure, pulse rate, and the concentration (MAC) of the halogenated agent in the expired air were recorded each minute. The time taken to reach conjugated gaze was recorded; at this time the vocal cords were sprayed with lidocaine and the trachea intubated. The time of tracheal intubation was recorded. Once the trachea was intubated the partial pressure of carbon dioxide in the expired air ($\mathrm{PE_{CO_2}}$) was continuously monitored using a Hewlett Packard 78345A monitor. This value was recorded each minute. All patients breathed spontaneously for the duration of the surgical procedure.

At the conclusion of the surgery, blood pressure, pulse rate, and $\mathrm{PE_{CO_2}}$ were again recorded. Anesthesia was then discontinued and the patient allowed to breathe 100% oxygen. Blood pressure, pulse rate, and $\mathrm{PE_{CO_2}}$ were again recorded each minute. Pharyngeal suction was repeated at regular time intervals and the time taken to respond to pharyngeal suction with a catheter and to react to the presence of the endotracheal tube noted. The trachea was then extubated and the patient's airway maintained by firm traction on the angles of the jaw. The time taken to the first verbal response was recorded. The results were compared using Student's *t*-test for unpaired data, and the null hypothesis was rejected when $P < 0.05$.

Results

There was no significant difference between the mean ages of the children or the mean duration of surgery between the two groups in the study.

Induction of Anesthesia

Blood pressure and pulse rate did not significantly differ between the groups during induction of anesthesia. The $\mathrm{PE_{CO_2}}$ measured on intubation of the trachea was similar in the two groups. In children receiving halothane, 1.5 MAC was reached in the expired air significantly more rapid than when using isoflurane (Fig. 1). The time taken to reach conjugate gaze and to achieve intubation of the trachea was significantly shorter in the halothane group (Fig. 2).

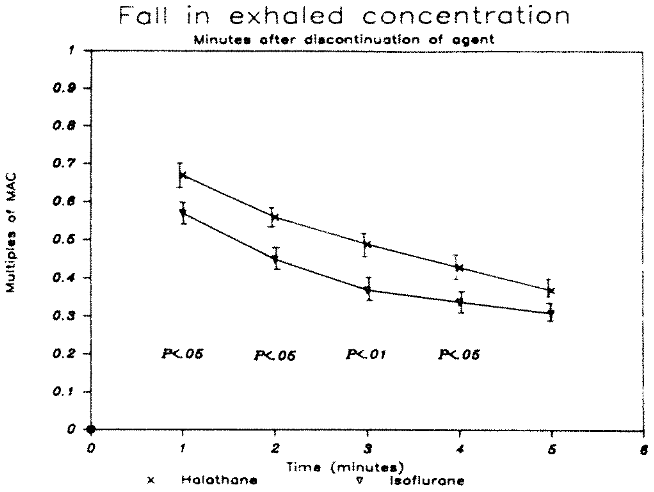

Figure 3. During recovery from anesthesia the concentration of isoflurane in expired gas decreased more rapidly than did the concentration of halothane. Values are expressed as multiples of MAC ± SEM.

Recovery from Anesthesia

During the recovery period blood pressure, pulse rate, and $P_{E_{CO_2}}$ did not differ between the two groups. The end tidal concentration of isoflurane decreased significantly more rapidly during recovery than did the concentration of halothane (Fig. 3). The times to respond to pharyngeal suction and to tracheal extubation and to the first cry did not differ between the groups.

Complications

Four patients given halothane developed transient cardiac dysrhythmias (two were nodal rhythms, two ventricular premature contractions). One patient given isoflurane developed bradycardia; this was associated with a stormy induction of anesthesia. Five of the 20 patients given isoflurane showed airway irritability as manifested by coughing or breath holding, while another developed postextubation laryngospasm. Only one patient given halothane developed breath holding.

Discussion

The purpose of this study was to evaluate the speed of induction of and recovery from anesthesia in unpremedicated pediatric outpatients using either halothane or isoflurane. When administering isoflurane to children between 1 and 12 yr of age, Joseph et al. (8) found that isoflurane produced a rapid induction of anesthesia and described what they felt was a low incidence of reflex activity. Their patients were older than the patients in our study and may have been better able to cooperate during induction of anesthesia. Their results indicate that either coughing, excessive secretions, laryngospasm, or breath holding occurred in 12 of the 66 patients studied (19%). In the investigation by Joseph et al. isoflurane was not compared with halothane, and the inspired concentration of administered agent was increased every 30 sec. In another pediatric study, Pandit et al. (7) compared induction of anesthesia using halothane and isoflurane but described the rate of administration of the halogenated agent as being "slow." It is difficult to determine, then, whether the rate of administration was similar for each agent or whether investigative bias could be excluded.

When calculating the MAC of the agents used, we recognized not only the difference in MAC between adults and children (11) but also the wide variation within the pediatric age group (12). As a result of this we used the MAC levels of isoflurane and halothane recorded for adults (10) and suggest that because there was no difference between the age groups of the children, that the error introduced by this assumption would be equal in each group. We attempted also to have a fixed end point (MAC 1.5) to anesthesia administration to exclude more rapid induction of anesthesia with the better tolerated agent by attaining a higher alveolar concentration in a given time period. Because the MAC of isoflurane is 50% greater than that of halothane, increases in the inspired concentration based on a percentage (rather than MAC) would result in smaller multiples of MAC in end-expired air over a specific time period. But in our study, the concentration of inhaled agent was increased every six breaths according to the patient's acceptance of the vapor. Isoflurane was thus delivered at a relatively smaller MAC, and it should have been possible to increase the concentration more rapidly than with halothane, which was not the case (Fig. 1).

We suggest that when measured at fixed time intervals the more rapid rise of halothane in the end-expired air compared with isoflurane was attributable to the higher incidence of coughing and breath holding (25%) in the isoflurane group, which undoubtedly prolonged the induction of anesthesia. During the recovery period, because an MAC of 1.5 for both agents was maintained for the duration of the surgical procedure, the rate of decrease of the agent in the end-expired air was dependent only on alveolar ventilation and on blood gas solubility. The rate of decrease of isoflurane in the expired air was more rapid during recovery from anesthesia in patients given isoflurane (as would be predicted from the lower blood gas solubility of the agent), but was of little practical significance because the time until response to pharyngeal suction, the time to extubation, and the time to phonation when maintaining traction on the angles of the jaw did not differ between the two groups of patients.

Because the end-expired partial pressure of carbon dioxide did not differ between patients receiving halothane or isoflurane either after induction of or during recovery from anesthesia, it is tempting to infer that respiratory depression was similar for both agents. This should be interpreted with caution because the effect of these agents on the cardiac output of our patients is not known. Blood pressure and pulse rate did not differ in the two groups during induction of or recovery from anesthesia.

In conclusion, when administering halothane or isoflurane to unpremedicated children using a technique in which the rate of administration was controlled, induction of anesthesia and tracheal intubation were more rapid with halothane. Recovery time was similar with the two agents. Patients given halothane had a high incidence of cardiac dysrhythmias, which were trivial and disappeared spontaneously. We conclude that in pediatric outpatients, isoflurane does not appear to offer any advantage over halothane in either induction of anesthesia or recovery from anesthesia.

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ANESTH ANALG
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Clinical Reports

A Regional Anesthetic Technique Compared to General Anesthesia for Outpatient Knee Arthroscopy

Nilesh J. Patel, MD, Michael H. Flashburg, MD, Sandor Paskin, MD, and Robert Grossman, MD

In 1973, Winnie et al. devised a technique for blocking the lumbar plexus, referred to as the "3-in-1 block," because with one injection the femoral, lateral femoral cutaneous (LFC), and the obturator nerves are blocked (1). The area of anesthesia includes the anterior, medial, and lateral thigh, as well as the periosteum of the femur, down to and including the knee (2–7). The "3-in-1 block" has been used clinically for operative management of fractures of the femoral shaft. It has been combined with sciatic nerve block for evaluation of acute knee injuries. Though not reported in the literature, the "3-in-1 block" would also appear to be useful for knee arthroscopy.

Our initial experience using the "3-in-1 block" for knee arthroscopy left two of five patients with pain on incision of the lateral side of the knee, an area innervated by the LFC nerve. Subsequently, we decided to test whether a separate, additional LFC nerve block would improve anesthesia for the procedure. In the present study, we compared the efficacy of the "3-in-1 block," with or without a separate LFC nerve block, with general anesthesia for knee arthroscopy in our ambulatory surgical center.

Materials and Methods

Ninety healthy patients (ASA class I) scheduled for outpatient arthroscopy of the knee joint were included in this prospective study after approval by our internal review board. Patients believed to need extensive posterior joint manipulation were not accepted for the study. All the patients were premedicated with 5–10 mg of diazepam orally 45–60 min prior to scheduled operating time. Additionally, patients receiving general anesthesia received 0.2 mg of glycopyrrolate intramuscularly 30–45 min prior to scheduled time of operation.

Thirty patients (group A) were selected randomly for operation under general anesthesia with nitrous oxide, narcotic, and oxygen; the remaining patients were randomly assigned to two equal groups, groups B and C. Patients in group B had both a "3-in-1 block" and a separate LFC nerve block, whereas those in group C had the "3-in-1 block" alone. The blocks were performed in the supine position using a 22-gauge needle with an electric nerve stimulator (7) after we prepared the groin with alcohol. Quadriceps contraction after electrical stimulation was used to identify the location of the femoral nerve (8). If 1 ml of local anesthetic (1.5% lidocaine or 1.5% mepivacaine) prevented the contraction, then 19 ml or 24 ml of the same solution was injected at the site in group B or C, respectively. In group B, an additional 5 ml of the same local anesthetic was injected in a fanwise manner, 2-cm medial and 2-cm caudad to the anterior superior iliac spine, above and below the fascia lata to block the LFC nerve. In patients of group C, 5 ml of normal saline was injected in a similar fashion. Epinephrine was not used with the nerve blocks.

A tourniquet was applied to the thigh, and surgical incision was made 20–25 min after injection of the local anesthetic in groups B and C. The incidence of pain was recorded in both groups as well as the need for supplementary anesthetic in the joint, which, if needed, was 10 ml of 1% lidocaine with epinephrine 1:200,000. Patients were given fentanyl, 100 μg, in-

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Table 1. Characteristics of Patient Population (mean ± SD)

	Group A	Group B	Group C
Age (yr)	30.8 ± 11.2	35.3 ± 16.7	34.0 ± 13.3
Weight (kg)	78.8 ± 12.8	75.8 ± 16.4	73.4 ± 13.3
Gender			
Male	19	18	15
Female	11	12	15
P	NS	NS	NS

Abbreviation: NS, not significant.

Table 2. Number of Patients Experiencing Pain on Incision in Groups B and C

Pain on incision	Group B	Group C	Total
Present	1	8[a]	9
Not present	29	22	51

[a] $P < 0.05$ using χ^2 for test of significance.

Table 3. Number of Patients Experiencing Postoperative Pain after Regional and General Anesthesia

Technique	Patients with pain	Patients without pain
Regional anesthesia	1	59
General anesthesia	8[a]	22
Total	9	81

[a] $P < 0.05$ using χ^2 for test of significance.

travenously if discomfort was present during the procedure.

All patients were monitored until discharge from our ambulatory surgical center. The incidence of postoperative nausea, vomiting, and pain was recorded in all the patients. Pain was determined by questioning the patient. Patients were considered ready for discharge on a score of 10 when 2 points each were assigned for stable vital signs, ability to retain fluids orally, ability to void, absence of pain or bleeding, and ability to walk. The time for completion of surgery to readiness for discharge was considered as recovery time and was recorded for all patients. Also, the surgeons' opinions regarding adequacy of muscle relaxation in groups B and C were recorded. Preference of anesthetic technique (regional vs general) for a similar procedure was also recorded for patients in group B and C. The results were analyzed using χ^2 and unpaired Student's t-test to determine significance. A P value less than 0.05 was considered statistically significant (9). Results are given as means ± SD.

Results

Patients in all three groups were comparable in age and weight (Table 1). Operative time was 42.1 ± 11.2 min. There were no complications in any of the groups. Eight of 30 patients in group C had pain on incision compared to only 2 of 30 in group B (Table 2) ($P \leq 0.05$). No patients in groups B and C had sensation to pin prick over the medial aspect of the knee, and all were unaware when an incision was made there. Those who experienced pain on lateral knee incision had supplemental local anesthetic injected intraarticularly by the surgeon, and the procedure was completed uneventfully.

In the postoperative period, before discharge from our ambulatory surgical center, only one patient in both groups B and C required analgesics for pain, compared to eight in group A (Table 3) ($P < 0.05$). The average discharge times from the ambulatory surgical center in groups B and C were 57.3 ± 9.2 min and 55.2 ± 9.6 min, respectively, whereas that for patients receiving general anesthesia (group A) was 95.3 ± 10.3 min (Fig. 1) ($P < 0.05$). Two patients in both groups B and C and five in group A experienced nausea, vomiting, or both; the difference was not statistically significant.

All surgeons were satisfied with the degree of muscle relaxation with either regional anesthetic technique and experienced no difficulty in manipulation of the knee joint. All but three patients having regional anesthesia expressed preference for the same anesthetic for a similar procedure, if needed in the future.

Discussion

The lumbar plexus is formed between two fascial planes, unlike the brachial plexus in the axilla, which is enveloped in a better defined sheath. The LFC nerve (L2, L3) is one of the earlier branches coming off the lumbar plexus. Thus a certain minimal volume of local anesthetic is needed to block the LFC nerve adequately, as shown by Winnie et al. (1). Our data indicate that anesthesia for arthroscopy of the knee joint is adequate with either a "3-in-1 block" alone or a "3-in-1 block" and LFC nerve block combined. Analgesia is more complete, however, when both nerve blocks are performed. All eight patients who experienced pain on incision in group C had analgesia over the inner aspect of the thigh (obturator distribution), i.e., the local anesthetic reached the lumbar plexus. The muscle relaxation produced with either regional technique was adequate, and both patients and surgeons were generally satisfied. Although all the patients in the study of Winnie et al. had good anesthesia of the lateral thigh, using a paresthesia as an endpoint for

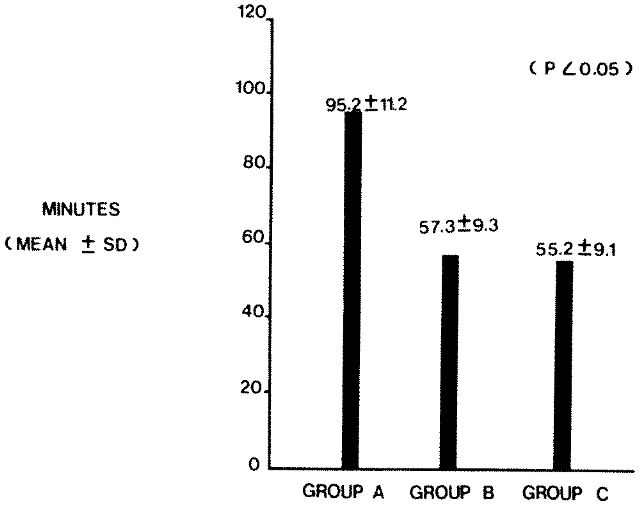

Figure 1. Recovery times.

local anesthetic injection, we found in the present study that a separate injection to anesthetize the LFC nerve was more effective in providing anesthesia for knee arthroscopy. We used a nerve stimulator for nerve identification. Electrical stimulation of the femoral nerve using a stimulator is painless and eliminates the momentary discomfort of eliciting a paresthesia. In our hands, the lateral side of the knee seemed more uniformly anesthetized with a separate LFC nerve block than with a "3-in-1 block" alone, based on the incidence of incisional pain.

The adequacy of anesthesia produced by either regional technique reduced the need for supplementary sedatives and analgesics both intraoperatively and postoperatively. Also, the short duration of the local anesthetic used decreased need for sedatives and narcotics significantly, and it reduced the recovery time compared to general anesthesia, enabling earlier discharge. Only two patients having regional anesthesia had postoperative nausea and vomiting; the need for postoperative analgesics was also significantly less. Regional anesthesia also allayed some of the fears of general anesthesia existing in many patients (postoperative nausea and the fear of not waking up again). Most of the patients whom we studied desired to see the arthroscopy on the television screen, which gave them both a better understanding of their disease and a sense of involvement. Reasons cited for refusal of regional anesthesia included anxiety and a fear of discomfort on being awake during the procedure. Most of the patients coming for outpatient surgical arthroscopy of the knee joint at our institution desire regional anesthesia and are informed of less pain when a "3-in-1 block" and a separate LFC nerve block are performed.

The "3-in-1 block" and LFC nerve blocks are simple to perform. The use of a nerve stimulator makes it easier to locate the femoral nerve, which lies 1.0–1.5 cm lateral to, and in a separate fascial sheath from, the femoral artery. The anatomy thereby reduces the chances of an intravascular injection. Femoral nerve block is also associated with minimal or no discomfort; there were no complications in the patients studied. Adequate anesthesia develops in 20–25 min, the time usually needed for preparation and draping of the knee. The blocks can be performed in a separate room to save time. The regional technique described above produces adequate anesthesia for such maneuvers as removal of plica, repair of menisceal tear, and shaving of cartilage.

In our hands, the "3-in-1 block" combined with lateral femoral cutaneous nerve block provides better anesthesia for outpatient knee arthroscopy than the "3-in-1 block" alone. It is a preferred technique for patients in whom general anesthesia is not desirable.

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ANESTH ANALG
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Anesthetic Management during Therapeutic Disruption of the Blood–Brain Barrier

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Central nervous system (CNS) malignancies respond poorly to peripherally administered chemotherapeutic agents (1). The primary reason for the poor response appears to be the existence of the blood–brain barrier (BBB) and the inability of most cancer chemotherapeutic agents to penetrate it.

Over the last 15 years, attempts have been made to reversibly disrupt the blood–brain barrier to allow lipid insoluble compounds with higher molecular weights to penetrate into the brain. CNS methotrexate levels 10–50-fold higher than those normally produced have been achieved in animal studies following barrier disruption (2). Osmotic BBB disruption with hypertonic solutions appears to be the most effective and reversible technique (3,4) and has been used in the treatment of a significant number of patients with both primary and metastatic CNS lesions with excellent results (5).

Currently, therapeutic BBB disruption is limited to clinical trials at relatively few medical centers. Although other treatment modalities exist, we describe our anesthetic experience with patients who present for BBB disruption in anticipation of this procedure becoming more widespread.

Methods

All patients presented to the Department of Neurosurgery with either primary or metastatic CNS lesions. Informed consent was obtained.

All patients were treated preoperatively with phenobarbital or phenytoin. Dosages of corticosteroids were decreased over several days before being discontinued prior to the disruption procedure. Cimetidine and all other medications not considered essential were discontinued due to the possibility of enhanced CNS effects after disruption. Premedication was achieved with oral diazepam, 0.1–0.2 mg/kg, and glycopyrolate, 0.2 mg intramuscularly, on call to the radiology suite.

Routine monitoring included an ECG, an indwelling arterial catheter, and a precordial stethoscope. A single 16-gauge peripheral venous line was obtained after local analgesia. Central venous access was obtained by routine methods when peripheral venous access was considered inadequate.

Anesthesia was induced with a combination of diazepam, 5–10 mg, fentanyl, 50–100 μg, pancuronium, 0.5–1.0 mg, and thiopental, 2–6 mg/kg intravenously. Tracheal intubation was performed after succinylcholine, 1–1.5 mg/kg intravenously, and ventilation controlled with 2:1 nitrous oxide:oxygen. All patients were hyperventilated to minimize intracranial blood volume. Ventilation was adjusted to maintain arterial P_{CO_2} between 25 and 30 mm Hg. Anesthesia was maintained with incremental doses of fentanyl and 0.25–0.5% isoflurane as necessary. Nasogastric tubes were placed to limit postanesthetic vomiting. A Foley catheter was required due to the diuresis after the use of mannitol as part of the disruption procedure.

The internal carotid or vertebral artery was then cannulated percutaneously using the femoral approach. Appropriate flow rates for intraarterial infusion of mannitol were determined radiographically, as that flow needed to totally replace internal carotid or vertebral blood flow for 20–30 sec without excessive reflux into the external carotid artery or the contralateral vertebral artery.

A diuresis was established with furosemide 10 mg intravenously. Cyclophosphamide, 20–50 mg/kg, was given intravenously over 10 min starting 20 min before the disruption procedure, so that it would be completed approximately 10 min prior to the BBB disruption. Cyclophosphamide must be metabolized by the liver in order to be active.

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Atropine in 0.2–0.4-mg increments was given intravenously until a modest increase in heart rate was produced. Thiopental, 2–4 mg/kg intravenously, and pentobarbital, 100 mg intravenously, were given immediately prior to disruption. Pentobarbital, 200 mg, was given if seizures occurred with prior disruptions.

Disruption was accomplished with 250–350 ml of 25% mannitol injected over 20–30 sec through the internal carotid or vertebral artery catheter. One minute later a radionucleotide was injected intravenously for subsequent brain scan documentation of the degree of disruption, after which the position of the internal carotid or vertebral artery catheter was rechecked before methotrexate (500–2500 mg) was given through the catheter within 5 min. Seizures after the methotrexate injection were treated with diazepam, 5–10 mg intravenously, or thiopental, 2–3 mg/kg intravenously. The angiographic catheter was then removed and pressure placed on the groin for 10 min. The patients were transported to the neurosurgical ICU, intubated, and were mechanically ventilated until awake, alert, and spontaneously able to ventilate well, at which time the endotracheal tube was removed.

Results

During the past 12 months, 60 BBB disruption procedures have been carried out in 15 patients. Ten patients are currently receiving monthly treatments. The lesions being treated include primary CNS tumors in thirteen patients and metastatic ovarian adenocarcinoma and metastatic adenocarcinoma of the prostate in one patient each. One patient died within 8 hr of her fifth disruption, apparently secondary to brain stem herniation. One patient died of progression of disease. Three other patients have discontinued treatment because of lack of response or for personal reasons. Of the remaining patients, 60–70% have improved depending on tumor type. One patient with a glioblastoma is believed to be in remission.

During the mannitol disruption, the ipsilateral face visibly blanched, and the pupil dilated. Bradycardia and hypotension occurred frequently and were followed by tachycardia and hypertension. Each was treated appropriately when necessary.

Six patients suffered seizures during the procedure, usually after intraarterial methotrexate was given. Seizure activity tended to recur with subsequent disruptions. Accordingly, those patients having a seizure were then routinely given additional pentobarbital or phenytoin prior to subsequent disruption procedures. The patients were generally extubated within 2–4 hr. A brain scan was obtained 3 hr after the disruption procedure to document its effectiveness. The patients were generally discharged 2–3 days after the procedure.

Discussion

Patients with space occupying intracranial lesions frequently have increased intracranial pressure (ICP) or reduced intracranial compliance. This has not, however, been found to be a significant problem during therapeutic disruption of the BBB. Animal studies have demonstrated a 1–1.5% increase in brain water after BBB disruption (6) whereas initial studies in patients in whom ICP was directly monitored demonstrated only mild and transient increases in ICP that did not exceed 10 mm Hg (7). Some patients have had an exacerbation of their preexisting neurologic deficit, probably secondary to a combination of steroid discontinuation and iatrogenic increase in ICP. However, the increase in neurologic deficit was generally transient, resolving in 48–72 hr. One of our patients died approximately 8 hr after a BBB disruption procedure. However, the procedure was performed in a patient already near death from tumor progression.

The discontinuation of corticosteroids prior to BBB disruption is necessary because of their ability to stabilize the BBB and thus to limit the disruption process (8). Although steroid withdrawal could increase ICP in patients with intracranial tumors, this has not proven to be a significant problem.

The decrease in heart rate and blood pressure seen immediately after mannitol infusion was presumably secondary to carotid sinus stimulation. Pretreatment with atropine effectively limited the degree of bradycardia and hypotension.

All our patients had peripheral arterial catheters inserted that, while facilitating monitoring of blood pressure, were actually placed at the request of the neurosurgeons for subsequent monitoring of blood pressure and for obtaining arterial blood samples. The marked diuresis (2–3 L/hr) produced by the mannitol required careful fluid monitoring and serial laboratory determinations to avoid hypokalemia and hyperglycemia.

The osmotic disruption of the BBB, which allows increased concentrations of chemotherapeutic agents to enter the brain parenchyma, almost certainly alters the effects of some of the drugs administered during anesthesia. No data are currently available on this issue, but it is one that warrants further investigation.

Although complete data are not yet available, it appears that the BBB disruption followed by appropriate chemotherapeutic agents may offer a means for both prolongation of life as well as improvement in the quality of life to a population of patients who traditionally have responded poorly to peripherally administered chemotherapeutic agents. It is a procedure which we anticipate will become more common and with which anesthesia personnel will need to be more familiar.

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Entrainment of Oxygen and Halothane during Jet Ventilation in Patients Undergoing Excision of Tracheal and Bronchial Tumors

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Sanders introduced the use of a Venturi injector for jet ventilation of patients undergoing bronchoscopy (1). The injector, attached to the open end of the bronchoscope, is used to deliver intermittent jets of oxygen. Oxygen jets entrain two to three times their own volume of ambient air, which in turn provides the pressure and volume necessary for adequate ventilation.

The principle of jet ventilation via a long narrow catheter that functions as an injector has been utilized for ventilation of patients undergoing tracheal or bronchial surgery (2–6). The technique, although providing adequate ventilation, may be associated with air entrainment that dilutes the inspired oxygen concentration and predisposes to aspiration of blood and debris into the ventilated lung. Also, it is difficult to administer inhalation anesthetics during jet ventilation, and anesthesia has to be maintained with intravenous techniques.

The present report utilizes the Venturi injector for jet ventilation of patients undergoing resection of tracheal or bronchial tumors. The injector is adapted to a long cuffed tracheal tube of small diameter, while the entrainment orifice of the injector is connected to the anesthesia circuit. The technique ensures a high inspired oxygen concentration and facilitates the administration of inhalation anesthetics.

Case Report 1

A 20-yr-old woman was completely symptom free until 2.5 yr ago when she started to complain of repeated episodes of cough, wheezing, and dyspnea. The patient was diagnosed as asthmatic but showed no response to antibiotic, corticosteroid, and bronchodilator therapy. The condition of the patient deteriorated, and she was admitted to the emergency room in severe respiratory distress. Arterial blood gas tension while breathing room air showed a P_{O_2} of 34 mm Hg and a P_{CO_2} of 34 mm Hg. Tracheal tomography revealed a filling defect suggestive of a tracheal tumor. Fiberoptic tracheoscopy under local anesthesia confirmed the presence of a cauliflower-like mass covered with normal mucosa. The mass obliterated 90% of the tracheal lumen and was arising from the left anterolateral wall of the trachea at the level of the eleventh tracheal ring.

The patient was scheduled for urgent thoracotomy for resection of the tracheal tumor and tracheal reconstruction. Premedication was limited to intramuscular atropine, 0.6 mg. In the operating room, the patient was preoxygenated with 100% oxygen for 5 min. Anesthesia was induced with thiopental (5 mg/kg) followed by succinylcholine (1 mg/kg). The trachea was intubated with a long cuffed tracheal tube (inner diameter 6 mm), the distal end of which was kept above the level of the tracheal tumor. A Venturi injector was adapted to the proximal end of the tracheal tube. The entrainment orifice of the injector was connected to the anesthesia circuit delivering O_2–halothane (Fig. 1). The pop-off valve of the anesthesia circuit was kept wide open. A flow of oxygen at a pressure of 50 psi was delivered via the injector. The oxygen flow was automatically interrupted by a solenoid valve controlled by an electronic timer. Intermittent oxygen jets were delivered at a rate of 20 per minute with an I:E ratio of 1:2. The oxygen jets entrained O_2–halothane from the anesthesia circuit in order to maintain a high level of inspired oxygen concentration and to administer the inhalation anesthetic. The concentration of halothane delivered by the vaporizer varied between 2 and 3%.

After we ensured adequate ventilation, a long-acting nondepolarizing muscle relaxant, alcuronium, was given to maintain neuromuscular block. The pa-

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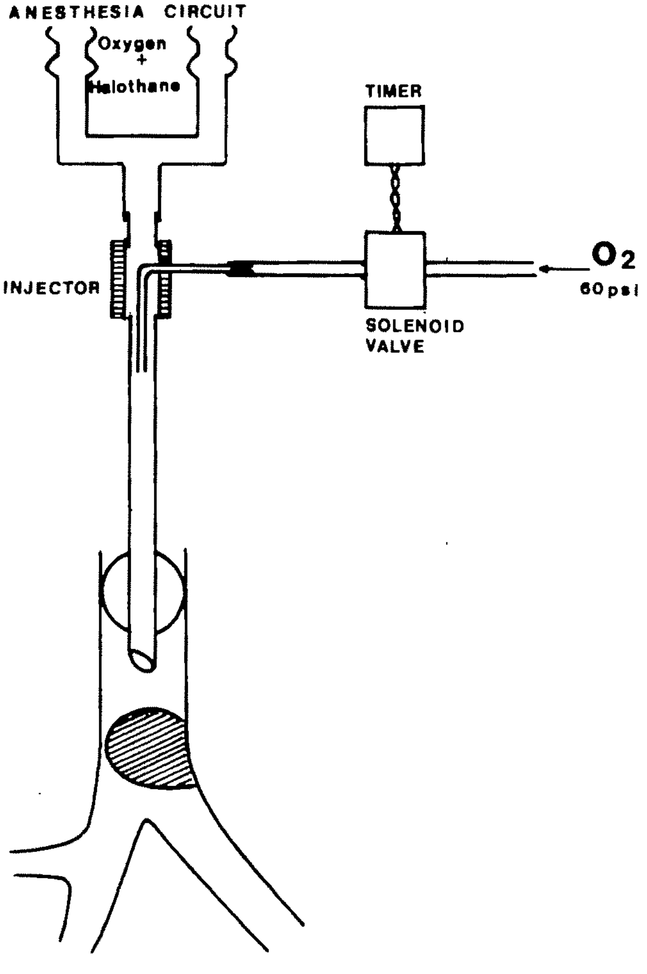

Figure 1. Diagram of system used for jet ventilation. The injector is connected to the cuffed tracheal tube on one side and to the anesthesia circuit on the other side. The injector is driven by intermittent jets of oxygen (50 psi) that are automatically interrupted by an electronic timer controlling a solenoid valve.

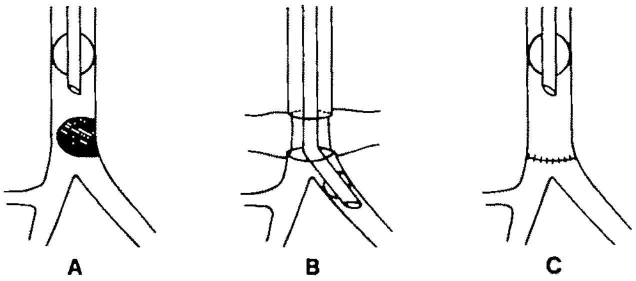

Figure 2. Diagram depicting the position of the tracheal tube before resection of the tracheal tumor (*A*), during tracheal reconstruction (*B*), and after completion of the anastomosis (*C*).

tient was then positioned in the lateral position, and a right posterolateral thoracotomy was performed. The mediastinal pleura over the distal trachea was opened at the site where the tumor was palpated. A 1-cm longitudinal incision over the tumor was performed, and under direct vision the tracheal tube was pushed down into the left main bronchus (Fig. 2*B*). The left lung was ventilated by jet ventilation, while the surgeon could easily resect the 2-cm segment of trachea involved by the tracheal tumor. Frozen section suggested the diagnosis of a carcinoid tumor. The trachea was reconstructed without tension. The tracheal tube was then withdrawn above the suture line, and jet ventilation of the two lungs was resumed (Fig. 2C). Arterial blood gas tensions before, during, and after tracheal reconstruction are shown in Table 1.

A posterior splint was applied to the head and neck to keep the neck flexed postoperatively in order to prevent tension on the anastomosis. At the end of the procedure, neuromuscular blockade was reversed with a mixture of atropine, 0.02 mg/kg, and neostigmine, 0.05 mg/kg, and the patient resumed adequate spontaneous breathing.

Case Report 2

A 42-yr-old woman was admitted with complaint of dyspnea on exertion, productive cough, wheezing, and stridor for 3 months. A chest x-ray showed hyperaeration of the left lung and right upper lobe. The right, middle, and lower lobes were atelectatic, with a shift of the mediastinum to the right. Lung tomography revealed a tumor obstructing the right main bronchus. The patient was scheduled for bronchoscopy and possible right pneumonectomy.

The patient was premedicated with glycopyrrolate, 0.4 mg, morphine, 5 mg, and promethazine, 25 mg, intramuscularly 60 min prior to surgery. After preoxygenation, anesthesia was induced with thiopental, 5 mg/kg, followed by succinylcholine, 1.5 mg/kg. Bronchoscopy revealed total occlusion of the right main bronchus by a tumor, the upper margin of which started about 3 mm distal to the carina. After bronchoscopy, the trachea was intubated with a 6-mm inner diameter cuffed tracheal tube that was connected by an injector to the anesthesia circuit, as illustrated in Figure 1. As in the first case, the patient was ventilated by intermittent oxygen jets delivered via the injector, while halothane–O_2 was entrained from the anesthesia circuit. Neuromuscular block was maintained by alcuronium.

A right postero–lateral thoracotomy was performed. The right main bronchus was opened transversally at the level of the carina, and the tumor was found to originate about 5 mm distal to the site of incision. The tracheal tube was pushed into the left main bronchus and jet ventilation of the left lung was

Table 1. Arterial Blood Gas Tensions (mm Hg) and pH before, during, and after Tracheal Reconstruction in Case 1

	F_{IO_2}	P_{O_2}	P_{CO_2}	pH
Spontaneous breathing (preoperative)	0.2	55	26	7.56
TLV (tube above tumor)	1.0	589	42	7.47
OLV (left bronchial intubation)	1.0	91	43	7.45
TLV (tube above anastomosis)	1.0	600	43	7.45
Spontaneous breathing (postoperative)	0.2	100	45	7.44

Abbreviations: TLV, two-lung ventilation; OLV, one-lung ventilation.

Table 2. Arterial Blood Gas Tensions (mm Hg) and pH before, during, and after Removal of the Bronchial Tumor and Reconstruction in Case 2

	F_{IO_2}	P_{O_2}	P_{CO_2}	pH
Spontaneous breathing (preoperative)	0.2	82	41	7.39
TLV (tube in the trachea)	1.0	601	27.6	7.50
OLV (left bronchial intubation during resection)	1.0	156	32	7.45
OLV (tube in the trachea after pneumonectomy)	1.0	500	30	7.46
Spontaneous breathing (postoperative)	0.2	90	47	7.36

Abbreviations: TLV, two-lung ventilation; OLV, one-lung ventilation.

continued. A right pneumonectomy was performed; the distal trachea and the right main bronchus were closed primarily with 3–0 prolene sutures. The tube was then withdrawn to the trachea, and jet ventilation was continued. At the end of the procedure, neuromuscular blockade was reversed using atropine, 0.02 mg/kg, and neostigmine, 0.05 mg/kg. Blood gas tensions before, during, and after reconstruction are showed in Table 2.

Discussion

Anesthetic management of patients undergoing surgical excision of tracheal or bronchial tumors is a challenge to anesthesiologists who must be able to ventilate the patients both before resection, despite obstruction of the airway by the tumor, as well as during resection and reconstruction when excessive air leakage occurs.

Induction of general anesthesia can be hazardous in these patients. Before resection of the tumor, the patient may be allowed to breathe spontaneously, using inhalation induction and maintenance of anesthesia. As soon as the airway is opened, anesthesia may be continued across the operative field by intubating the distal trachea or the main bronchus by sterile tubings connected to the anesthesia circuit (7). In patients with severely obstructing tumors, a small endotracheal tube can be insinuated past the mass at the margin where tumor infiltration is not present (7). However, this technique may be risky, because the tube may traumatize the tumor and cause bleeding that can cause complete obstruction. Also, a tube small enough to pass in the obstructed trachea may not improve the airway because the thickness of the walls of the tube may encroach on the available tracheal lumen. Cardiopulmonary bypass has been used for the management of patient having near total tracheal occlusion or carinal resection (8). However, the need for heparinization may present dangers when the resection and dissection are extensive and complicated (7).

Jet ventilation is effective in the presence of tracheal stenosis (9) or airway disruption (10) and has been used for ventilating patients undergoing tracheal and carinal reconstruction (2–6). Ventilation can be achieved readily by intermittent oxygen jets delivered via a long thin catheter that functions as an injector. The technique provides the surgeon with an unobstructed field and ensures adequate ventilation during tracheal reconstruction. However, the catheter often cannot be fixed in the appropriate position, and the danger of soiling of the ventilated lung by blood or debris from the surgical field is present. Also, the oxygen jets can entrain room air that dilutes the inspired oxygen concentration and does not allow inhalation techniques of anesthesia. The use of high frequency jet ventilation can minimize air entrainment and prevents aspiration of blood and debris into the open bronchus (4,5).

To facilitate the administration of inhalation anesthetics and to ensure a high inspired oxygen concentration, we used the injector as an interface between the tracheal tube on one side and the anesthesia circuit on the other side. A long cuffed tracheal tube of a small internal diameter (5–6 mm) was used, which could be pushed into the distal trachea or the main bronchus during resection of the tumor and subsequent reconstruction. The small size of the tracheal tube makes it desirable to use jet ventilation. The pop-off valve of the anesthesia circuit is kept widely open during jet ventilation because ventilation does not depend on positive pressure applied via the circuit, but rather on entrainment from the circuit; this will ensure safety if the solenoid valve is accidentally stuck open.

The technique provides adequate ventilation before and after resection of the tumor, and it allows surgery to be performed easily and in an unhurried manner. Also, the jet, instead of entraining room air, entrains oxygen and inhalation anesthetics from the anesthesia circuit, which is connected to the entrainment orifice of the injector. This facilitates the administration of inhalation anesthesia whenever desired and ensures a high inspired oxygen concentration.

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Effect of Preanesthetic Ranitidine and Metoclopramide on Gastric Contents in Morbidly Obese Patients

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Obesity ranks as one of the most common medical disorders in the United States (1). Extremely obese patients face an inordinate risk for aspiration of gastric contents because of the combination of increased gastric volume, reduced gastric pH, increased intraabdominal pressure, and an increased incidence of hiatus hernia (2,3). In recent years, several investigators have demonstrated the efficacy of H_2-receptor antagonists and metoclopramide for the reduction of gastric acidity and volume in various subgroups of surgical patients (4–8). Because the effects of ranitidine, metoclopramide, or both have not been studied in morbidly obese patients, we undertook this prospective investigation to evaluate the effect of ranitidine (150 mg or 300 mg) alone and in combination with metoclopramide (10 mg or 20 mg) on gastric acidity and volume in morbidly obese patients undergoing elective surgery.

Materials and Methods

Fifty morbidly obese adult inpatients scheduled for elective surgery were studied. Morbid obesity was defined as 100 lbs (45.5 kg) above ideal weight (3,9). All patients fasted for a minimum of 8 hr, and none had any gastrointestinal disorders. Obese patients were randomly allocated into five groups with 10 patients in each group. Patients in group I received neither ranitidine nor metoclopramide and served as controls. group II patients received ranitidine, 150 mg orally, the night before and on the morning of surgery, whereas patients in group III received metoclopramide, 20 mg orally, on the morning of surgery in addition to ranitidine as in group II. Patients in group IV received ranitidine, 300 mg orally, the night before and on the morning of surgery, whereas group V patients received metoclopramide, 10 mg orally, the morning of surgery in addition to ranitidine as in group IV. All patients were premedicated with diazepam, 10 mg orally; meperidine, 75 mg intramuscularly, and hydroxyzine, 75 mg intramuscularly, 45–90 min prior to induction of anesthesia. The protocol for this investigation was approved by the Institutional Review Committee, and informed consent was obtained from all the patients.

After satisfactory induction of anesthesia with thiopental and endotracheal intubation with the aid of succinylcholine, a #18 Salem sump was passed into the stomach, and all available gastric contents were aspirated by suction into a mucus trap. The position of the gastric tube was confirmed by insufflation of a small amount of air into the stomach through the Salem sump with simultaneous auscultation over the epigastrium. The pH was determined by a Corning pH meter using an Ag/Agcl probe combination electrode.

Patients with a gastric pH ≤ 2.5 and a volume of ≥ 25 ml were defined to be at potential risk of pulmonary damage in the event of aspiration. These factors were analyzed in combination and independently.

Statistical analyses were performed by analysis of variance (ANOVA) and the χ^2-test. One way analyses of variance with Duncan's multiple range follow-up tests were used to test the statistical significance of differences among the means of the five groups. Two way (2 × 2) ANOVAs were performed on data for the four experimental groups (groups II–V) to test the effects of ranitidine dosage both with and without the addition of metoclopramide. Overall 5 × 2 χ^2-tests of independence with 2 × 2 χ^2 follow-up tests were used to test the significance of differences among the proportions at risk in the five groups. Results were considered statistically significant if the P values were less than 0.05.

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Table 1. Patient Characteristics[a]

	Number of patients	Age (yr)	Height (cm)	Weight (kg)	Body mass index (weight in kg/height in m^2)
Group I, control	10	42.7 ± 4.1	166.6 ± 2.3	112.3 ± 3.4	40.4 ± 0.6
Group II, ranitidine (150 mg hs & AM)	10	46.4 ± 5.4	162.8 ± 1.8	111.1 ± 3.4	41.9 ± 0.9
Group III, ranitidine (150 mg hs & AM) + metoclopramide (20 mg, AM)	10	47.7 ± 4.1	160.3 ± 2.0	113.5 ± 3.5	44.1 ± 0.7
Group IV, ranitidine (300 mg, hs & AM)	10	42.8 ± 4.6	164.1 ± 1.7	109.8 ± 2.9	40.8 ± 0.8
Group V, ranitidine (300 mg, hs & AM) + metoclopramide (10 mg AM)	10	52.2 ± 3.4	166.4 ± 2.6	116.0 ± 5.7	41.7 ± 0.9
Direction and significance of values		NS	NS	NS	III > I = II = IV = V

[a]Values are means ± SEM. NS, not significant.

Table 2. Mean (± SEM) Values for Duration of Fasting, Drug Dosages, and Time Intervals from Drug Administration in Morning to Gastric Sampling

	Fasting period (hr)	Ranitidine dosage (mg/kg)	Metoclopramide dosage (mg/kg)	Time from ranitidine and metoclopramide administration in AM to collection of gastric sample (min)
Group I	11.9 ± 0.5	—	—	—
Group II	9.9 ± 0.5	1.36 ± 0.04	—	143 ± 14.8
Group III	9.6 ± 0.4	1.33 ± 0.04	0.178 ± 0.006	143 ± 12.3
Group IV	10.6 ± 0.6	2.75 ± 0.07	—	164 ± 16.3
Group V	10.7 ± 0.7	2.63 ± 0.11	0.088 ± 0.004	182 ± 16.3
Direction and significance of values	I > II = III I = IV = V II = III = IV = V	IV = V > II = III	III > V	NS

NS, not significant.

Results

Statistical information concerning patient characteristics, fasting periods, and drug administration for the five groups is presented in Tables 1 and 2. Sex distribution, age, height, weight, and time from morning administration of ranitidine and metoclopramide to gastric sampling were similar among the five groups. However, the control group (group I) had a significantly longer fasting period than groups II and III. Group III had a significantly higher mean body mass index (weight in kg/height in m^2) than the other four groups, which did not differ significantly in the other groups.

Gastric pH

There were significant differences among the five groups with respect to mean gastric pH (Table 3). The four experimental groups (groups II–V) had a significantly higher gastric pH than the control group (group I), and the four experimental groups did not differ significantly.

The proportion of patients with pH ≤2.5 differed significantly in the five groups (Table 3). The four experimental groups had significantly fewer patients (none) with pH ≤2.5 than the control group, and there were no significant differences among the four experimental groups. The same pattern of results was found for the proportion of patients with pH ≥5.0.

Gastric Volume

Mean gastric volume was significantly lower in the four experimental groups than in the control group and was not significantly different in the four experimental groups (Table 4). However, the pooled mean

Table 3. Gastric pH Characteristics

	Mean ± SEM	Range	Patients with pH ≤2.5	Patients with pH ≥5.0
Group I	2.32 ± 0.38	1.50–5.40	8 (80%)	1 (10%)
Group II	7.17 ± 0.12	6.72–8.00	0 (0%)	10 (100%)
Group III	7.27 ± 0.13	6.75–8.05	0 (0%)	10 (100%)
Group IV	6.96 ± 0.14	6.52–7.99	0 (0%)	10 (100%)
Group V	7.20 ± 0.18	6.02–7.99	0 (0%)	10 (100%)
Direction and significance of values	I < II–V		I > II–V	I < II–V

(7.0 ml) of the two groups receiving metoclopramide (groups III and V) was significantly less than the pooled mean (16.5 ml) of the two groups that received ranitidine alone (groups II and IV).

There were significant differences among the five groups with respect to proportions of patients with gastric volumes ≥25 ml. There were significantly fewer patients (none) with gastric volumes ≥25 ml in the two groups receiving metoclopramide (groups III and V) than in two of the three groups not receiving metoclopramide (groups I and II). Although fewer patients (none) had gastric volume ≥25 ml in metoclopramide groups than in the third nonmetoclopramide group (group IV), the difference was not statistically significant.

The groups also differed significantly with respect to proportions of patients with gastric volumes ≥50 ml and ≥100 ml. There were significantly lower proportions of patients in groups III, IV, and V than in group I, with gastric volumes ≥50 ml. However there were no significant differences among the groups of proportions of patients with gastric volumes ≥100 ml.

Combined Risk of pH and Volume

The four experimental groups had significantly fewer patients (none) with gastric volumes ≥25 ml and pH ≤2.5, as well as gastric volumes ≥50 ml with pH ≤2.5 than did the control group (Table 4), but the four experimental groups did not differ significantly from each other. There were thus significantly fewer patients at risk in groups II, III, IV and V than in group I.

Comparison of Obese and Nonobese Controls

The control group of obese patients (group I) was compared with a control group of nonobese patients taken from a previous study in which similar methods were used (4). The obese patients were significantly heavier and had a significantly greater body mass index than nonobese patients (Table 5). In addition, the obese patients had a significantly higher mean gastric volume and a significantly greater proportion of patients with volume ≥100 ml than the nonobese patients.

Discussion

According to most investigators, a gastric pH below 2.5 and a volume of 25 ml or greater are considered critical factors for the development of pulmonary damage in adults in the event of aspiration (10,11). Vaughan et al. (3) demonstrated that a significant number of morbidly obese patients were at risk of aspiration. A total of 88% of them had gastric pH below 2.5; 85% had gastric volume greater than 25 ml at the time of induction of anesthesia. A linear increase in intraabdominal pressure with increasing weight (12) and increased incidence of hiatus hernia (13) has also been reported in obese patients. In addition, Vaughan et al. (3) hypothesized that abdominal fat, functioning as an extra peritoneal mass in morbidly obese patients, could prolong gastric emptying time further, leading to an increase in gastric volume which in turn may lead to antral distention, promoting gastrin release with subsequent increased parietal cell secretion. They also consider morbidly obese patients as having potentially full stomachs (3). Thus obese patients are considered to be at increased risk of potential aspiration and pneumonitis should aspiration occur.

The data from this study confirm the potential risk of acid aspiration despite overnight fasting in morbidly obese individuals having elective surgery, as 80% of the patients in the control group had a pH ≤2.5 and 70% of the patients had gastric volumes ≥25 ml, while 60% of the patients had a combination of pH ≤2.5 and volume ≥25 ml. In addition, 40% had gastric volumes ≥50 ml and 30% had volume ≥100 ml with pH ≤2.5. Ranitidine, 150 mg or 300 mg, administered orally the night before surgery and in the morning with or without metoclopramide, increased gastric pH ≥5.0 in all patients in the four experimental groups and reduced mean gastric volume in all groups. However, ranitidine, 150 mg and 300 mg, reduced the proportion of patients with volume ≥25 ml to 40 and 20%, respectively. Metoclopramide, 10 mg or 20 mg, in conjunction with ranitidine significantly reduced mean gastric volume and also reduced the proportion of patients with volume ≥25 ml to 0%. There was no difference among the four experimental groups with

Table 4. Gastric Volume Characteristics

	Volume (ml)		Patients with volume ≥25 ml	Patients with volume ≥25 ml and pH ≤2.5	Patients with volume ≥50 ml	Patients with Volume ≥50 ml with pH ≤2.5	Patients with volume ≥100 ml	Patients with volume ≥100 ml and pH ≤2.5
	Mean ± SEM	Range						
Group I	71.0 ± 24.0	8–200	7 (70%)	6 (60%)	4 (40%)	4 (40%)	3 (30%)	3 (30%)
Group II	20.1 ± 5.3	5–50	4 (40%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)
Group III	8.9 ± 2.5	1–22	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Group IV	12.9 ± 4.2	2–45	2 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Group V	5.2 ± 1.2	2–12	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Direction and significance of values	I > II–V		I > III–V II > III = V I = II II = IV	I > II–V	I > III–V II = III = V I = II	I > II = V	NS	NS

NS, not significant.

Table 5. Comparison of Control Nonobese Patients with Morbidly Obese Control Patients

	Control nonobese patients (*n* = 25)[*]	Control morbidly obese patients (*n* = 10)	Direction of results
Weight (kg, mean ± SEM)	64.9 ± 3.7	112.3 ± 3.4	O > NO
Height (cm, mean ± SEM)	167.5 ± 1.7	166.6 ± 2.3	NS
Body Mass Index (mean ± SEM)	20.4 ± 0.4	40.4 ± 0.6	O > NO
Gastric pH (mean ± SEM)	2.89 ± 0.38	2.32 ± 0.30	NS
Patients with pH ≤2.5	16(64%)	8(80%)	NS
Gastric Volume (ml, mean ± SEM)	22.3 ± 3.8	71.0 ± 24.0	O > NO
Patients with pH ≤2.5 and vol ≥25 ml	7(28%)	6(60%)	NS
Patients with pH ≤2.5 and vol ≥50 ml	2(8%)	4(40%)	NS
Patients with pH ≤2.5 and vol ≥100 ml	0(0%)	3(30%)	O > NO

[*] Data from Reference 4.
O, obese; NO, nonobese.

respect to gastric pH. The addition of metoclopramide to both regimens had a favorable effect on gastric volume.

Compared to previous studies (3,6), a similar proportion of morbidly obese patients were found to be at risk in the control group. However, although we found differences between obese and nonobese patients, our results do not agree with those of Vaughan et al. (3). They reported that none of the nonobese patients had both gastric content volume ≥25 ml and pH ≤2.5. Comparison of the results in this study with those of Wilson et al. (6) in their study of the effects of atropine, glycopyrrolate, and cimetidine in morbidly obese patients, shows that ranitidine appears to be slightly superior to cimetidine with respect to its effect on gastric pH. Results in the present study are also similar to our previous studies in nonobese patients with regard to the effects of both ranitidine and metoclopramide (4,5).

The technique employed in this study for the collection of gastric contents is subject to criticism in that the exact location of the gastric tube is not known at the time of aspiration of gastric contents and, consequently, all contents may not be obtained. As a result, gastric volumes may be underestimated. However, any underestimation would be consistent across treatment groups as the comparisons of group means and group proportions at risk are equally biased by the use of the technique. Another criticism of our study may be directed against the longer fasting period in the control group relative to groups II and III. However, the difference in the fasting period (11.9 hr and 9.9 and 9.6 hr, respectively) would not seem to be sufficient to account for the differences in gastric content.

Ranitidine is a highly selective H_2-receptor antagonist, more potent than cimetidine with longer duration of action and presumably with minimal side effects. Metoclopramide is a substituted benzamide with powerful effects on the lower esophageal sphincter, gastrointestinal motility, and vomiting center in the brain stem. Both drugs are available in both oral and parenteral forms. It is interesting to note that the usual adult doses of ranitidine (150 mg or 300 mg) and metoclopramide (10 or 20 mg) have had similar effects on gastric contents in the reduction of gastric acidity and volume in both nonobese (4,5) and morbidly obese individuals. This observation is an indication that the pharmacodynamic effects of these drugs are related to ideal weight or lean body mass rather than actual weight, which includes a high proportion of body fat relative to lean body mass in morbidly obese patients. However, we are not aware of any data referable to fixed drug pharmacokinetics in general and ranitidine and metoclopramide in particular in morbidly obese patients.

In summary, the risk of aspiration of gastric contents and acid pneumonitis in morbidly obese patients is significantly decreased by the oral administration of ranitidine (150 mg or 300 mg) at bedtime and on the morning of surgery plus metoclopramide (10 mg or 20 mg) in the morning of surgery to reduce gastric acidity and volume.

We are grateful to the hospital administration and the anesthesia, operating room, and laboratory staffs for their support and help. We also want to thank Wanda L. Hurt for secretarial help and Stephen J. Markwell for assistance in statistical analysis.

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Tourette Syndrome:
Anesthetic Implications

John E. Morrison Jr, MD, and Charles H. Lockhart, MD

Tourette Syndrome (TS), familiar to physicians as a condition in which patients may exhibit coprolalia (profane vocalizations) and echolalia (repetitious speech), is actually a complex neuropsychiatric disorder of lifelong duration with onset during childhood (1). The symptoms of TS begin as attention-deficit disorders and progress clinically into spasmodic, repetitious, stereotyped movements known as "tics" (2), often leading to confusion between TS and tic douloureux (trigeminal neuralgia). In advanced TS, muscle jerking, a more extreme example of tics, can vary from mild jerking of the upper part of the body to more obvious ballistic-type movements that are exacerbated by stress and a variety of other stimuli.

Two cases are presented that characterize the broad spectrum of clinical manifestations seen in TS and emphasize the problems confronting the anesthesiologist when such patients require elective or emergency surgery.

Case 1

A 28-yr-old male with TS was scheduled for retinal surgery after an injury sustained when he was banging his head against a wall during an emotional outburst. His routine medications were haloperidol and clonidine; he maintained reasonable control of his emotional lability, except when particularly stressed. The patient's most pressing concern was that he might "lose control" in the operating room, due to his anxiety in anticipation of the operation, or during his emergence when he might physically hurt the medical personnel caring for him. He also had great fear of having a mask placed on his face and felt that he could not tolerate it. He had a past history of asthma, with no recent exacerbations, and had undergone general anesthesia as a child for an appendectomy without difficulty. Physical examination was unremarkable with the exception of his ophthalmic pathology, and no wheezing was noted.

After a prolonged preoperative interview, during which the patient had the opportunity to discuss in depth his concerns about his specific anesthetic management and establish a personal bond with his anesthesiologist, he received repeated assurances that his status was not particularly threatening to the anesthesia staff. He was given his standard morning medication of haloperidol and clonidine and then premedicated with morphine sulphate, 10 mg, and hydroxyzine pamoate (Vistaril), 75 mg intramuscularly. Induction of anesthesia was accomplished with intravenous fentanyl, 50 μg, and thiopental, 500 mg, plus *d*-tubocurarine, 3 mg, followed by succinylcholine, 100 mg, to facilitate tracheal intubation. Anesthesia was maintained with enflurane, nitrous oxide, and oxygen. The anesthetic was uneventful, and droperidol was given in the postanesthetic recovery area for continued symptomatic control of his behavior.

Case 2

A 12-yr-old male was scheduled for elective repair of his inguinal hernia. He had been diagnosed as having TS several years after a distressing and protracted period of time before his hyperactivity and emotional lability were recognized as TS. His family had traveled extensively for numerous medical consultations and opinions, and were now well established using a holistic approach that seemed to provide best for the patient's needs as well as for their own needs. The patient took no medications because they previously had been unsuccessful in controlling his symptoms or had unacceptable side effects. His exacerbations were triggered by exposure to aromatic hydrocarbons (e.g., perfumes, noxious odors), and the family was extremely worried about his exposure to inhalational anesthetic agents. During the preoperative interview and tour of the operating area, he exhibited some

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ballistic movements of his arm and also had some mild vocalizations resembling grunting.

At the family's request, his holistic physician was contacted and expressed the belief that halothane and thiopental were not specific "triggering agents." With that reassurance, as well as the avoidance of perfumes, etc., among the operating personnel, and with the provision for postanesthetic recovery in an isolation room where he would not be distressed by other patients nor have to worry about his own emergence behavior, he underwent an uneventful general anesthetic. No premedication was given. Thiopental, 160 mg, was administered through an intravenous catheter started in the operating room, and anesthesia consisted of halothane, nitrous oxide, and oxygen by mask. His postoperative course was uneventful, and he was discharged the following morning.

Discussion

These two patients typify the diversity of the clinical manifestations seen in TS. Cohen et al. (1) have described this entity as an exemplary neuropsychiatric disorder of childhood reflecting an interaction among genetic, neurophysiologic, behavioral, and environmental factors. Most commonly seen in males, the progression through several phases, as first described by Gilles de la Tourette in 1885, begins with muscular jerking (usually of the head, neck, or arms), followed by inarticulate vocalizations or cries (often expressed as coughing, throat clearing, grunting, and even barking), later evolving in some 53% to the demonstration of coprolalia (obscenities) or more rarely echolalia (echoing back), according to Shapiro and Wayne (3). In a general review of childhood tics, Schowalter notes that these patients often exhibit compulsive licking, touching, biting, and other complex rituals, even though attempting to camouflage their tic behavior (2). Such motion might be confused with seizure-like activity during induction or emergence of anesthesia. While intelligence is generally above average, nonspecific EEG abnormalities are seen in about one-half of the patients.

Graphic descriptions of early case vignettes by Cohen et al. (1) testify to the severe emotional stresses experienced by patients with TS and their families, particularly during the nondiagnostic period, when patients and families experience extreme frustration because of the increasingly disturbing behavioral and somatic progression of the unusual symptoms. This period often results in a sense of mistrust of the medical profession, and fear of having to adapt to too rigid a protocol within a hospital environment. The sense of losing control when confronted with a highly emotional and stressful situation is frequently quite disturbing to these patients and their families. This can be a major problem for the anesthesiologist as suggested in the above case reports with their diversity of problems (i.e., the purely holistic approach of one patient, and the heavy medication preference of the other). It is extremely important to appreciate the sense of apprehension that exists in the patient and the family, and to provide them with an adequate opportunity to convey to the anesthesiologist their specific concerns about the hospitalization. Ample time must be set aside for the anesthesiologist to accomplish a personal preanesthetic consultation with the patient and family and to listen to their explanation of TS and to identify their own specific behavioral mannerisms. This time-consuming visit provides the strongest identification between the anesthesiologist and the patient with TS and establishes a relationship that will contribute much to the administration of a successful anesthetic. It appears from the experiences of the two patients described, that the specific anesthetic chosen is less important per se, than the general approach taken to the patient by the operating room team. We noted no clinical abnormalities that we would associate with atypical EEG activity, but such testing was not performed perioperatively on these two patients.

At present haloperidol, a butyrophenone, and, more recently, clonidine, an α-2-adrenergic agonist, are the most effective and frequently used medications for symptomatic control of TS. However, side effects such as extrapyramidal tract signs, cognitive blunting, and lethargy often restrict the clinical use of these medications. More recently, pimozide (Orap, McNeil Pharmaceuticals), a neuroleptic agent, has been approved by the FDA for TS patients with unresponsive or otherwise uncontrollable tics (4). Of note, however, is the occurrence of sudden unexpected deaths in patients given high-dose pimozide medication (greater than 0.3 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ or 20 mg/day) attributed to arrhythmias secondary to the QT interval prolongation seen in electrocardiograms of patients receiving pimozide. A recent review of the effect of prolonged QT interval syndrome by Galloway and Glass (5) outlines the perioperative implications for the anesthesiologist and some recommendations for both prevention and treatment. The development of tardive dyskinesia might also be expected with this medication.

In summary, patients with the diagnosis of Tourette's syndrome present a unique challenge to the anesthesiologist. The complex social and behavioral problems associated with this syndrome and the diversity of clinical scenarios require a thorough preoperative evaluation of these patients. The personal contact between the anesthesiologist and the patient and family constitutes the basis for a successful anesthetic, allaying their fears and establishing a bond that greatly reduces the exacerbations of the patient's motor symptoms resulting in a much smoother perioperative course. Particular attention must be given to the patients' medication regimen, especially if the neuroleptic pimozide is being used for symptomatic control, in view of its association with prolonged QT interval syndrome in higher dosages. The motor aspects of the advanced forms of tics (e.g., grunting, ballistic motions of the arms, etc.) should not be confused with atypical or complex seizure-like activity during the perioperative period.

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Loss of Cortical Evoked Responses due to Intracranial Gas during Posterior Fossa Craniectomy in the Seated Position

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Thomas G. Luerssen, MD

Sensory evoked responses (SERs) are frequently monitored to assess the integrity of neural pathways at risk for injury during surgical procedures. To be clinically useful, intraoperative SERs must not only be sufficiently sensitive to detect early injury but should also spare the operating team frequent disruptive false alarms. Because concern has been raised over the occurrence of "false positive" results, i.e., loss of the evoked response waveform in the absence of neurologic injury (1), we call attention to a previously unreported artifactual cause for the loss of the cortical somatosensory evoked potential (SSEP) during posterior fossa craniectomy in the seated position.

Case Report

A 15-yr-old male patient presented with a long history of headache, nausea, vomiting, and weight loss. Physical examination revealed growth retardation, absence of secondary sex characteristics, ataxia, paralysis of conjugate upward gaze, and bilateral papilledema. An endocrine evaluation confirmed the presence of panhypopituitarism, including diabetes insipidus, requiring replacement therapy with thyroid hormone, adrenocortical steroids, and vasopressin. Computerized tomography demonstrated a pineal mass and attendant obstructive hydrocephalus. A ventriculo–peritoneal shunt was inserted with relief of the symptoms associated with increased intracranial pressure. Two weeks later he was scheduled for craniectomy and biopsy of the pineal mass. The safest approach to the tumor was deemed to be supracerebellar and infratentorial, performed with the patient in the seated position.

On the morning of surgery, the patient was brought to the operating room unpremedicated. After induction of anesthesia with sodium amytal (5 mg/kg), fentanyl (30 μg/kg), and relaxant, the trachea was intubated without difficulty. The lungs were mechanically hyperventilated to maintain an arterial P_{CO_2} of 26–30 mm Hg. Anesthesia was maintained with 60% nitrous oxide (N_2O) in oxygen, 0.2% isoflurane and fentanyl by continuous infusion (3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$). Monitoring devices included a radial arterial cannula, an appropriately positioned multiorificed central venous catheter for aspiration of air, and a precordial Doppler. Because of the proximity of the mass to the upper midbrain, bilateral median nerve SSEPs were monitored using a Pathfinder II Electrodiagnostic Monitoring System (Nicolet Biomedical, Madison, WI). Stimuli were delivered to the median nerves at the wrist via platinum subdermal needles at a rate of 4.1 stimuli/sec. Evoked responses were recorded from gold disk electrodes positioned over the ipsilateral brachial plexus at Erb's point and over the contralateral sensory cortex, 2 cm posterior to the C3 and C4 positions (International 10–20 system). All active electrodes were referenced to an electrode on the forehead (FPz), and the ground electrode was located over the mastoid process. Bandpass filters were set at 30 and 250 Hz. Baseline SSEPs were obtained shortly after induction with the patient in the supine position. Repeat SSEPs obtained with the patient in the seated position were unchanged from baseline (Fig. 1). SSEPs were recorded at approximately 10-min intervals throughout the procedure.

A suboccipital craniectomy was performed. The dura was then opened so that it was hinged superiorly on the transverse sinus. Ten minutes later, during dissection of the superior cerebellum from the tentorium, a marked reduction in cortical SSEP amplitude (initially without a change in latency) was noted bilaterally. Shortly thereafter, the cortical SSEP was no longer recognizable (Fig. 1). Adequate stimulus delivery was verified by the persistence of the Erb's

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The opinions expressed herein are those of the authors and are not to be construed as reflecting the views of the Navy Department, of the Naval Service at large, or of the Department of Defense.

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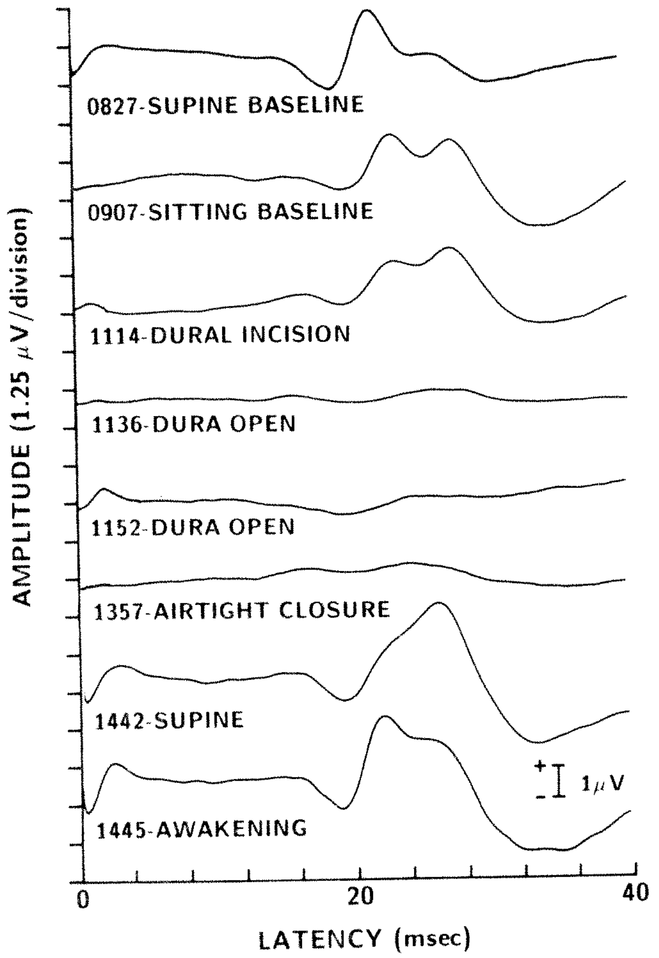

Figure 1. Cortical evoked response waveforms recorded during the procedure.

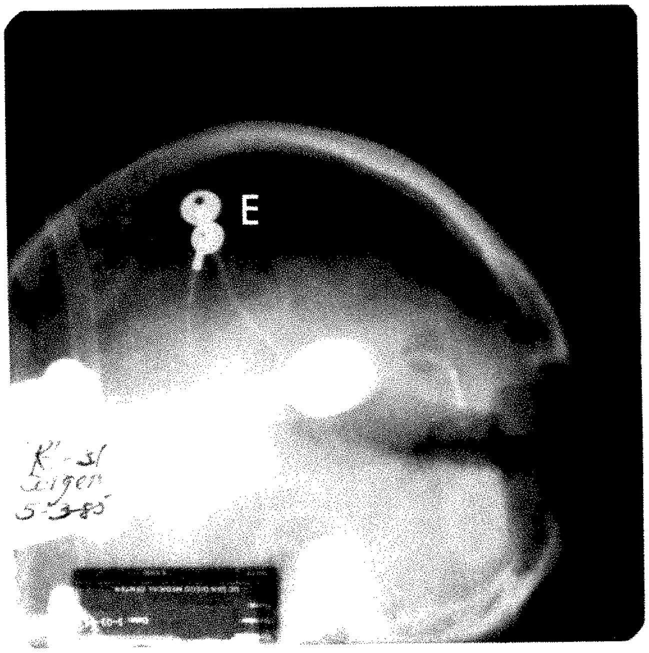

Figure 2. Lateral skull x-ray film obtained with the patient in the seated position at the time of achieving an airtight seal of the intracranial compartment. A large accumulation of gas is seen over the vertex. The cortical electrodes (E) appear to overlie the intracranial gas pocket.

point potential. The recording equipment was checked for electrical malfunction. Electrode impedances continued to measure less than 3 kOhms. There were no changes in blood pressure (mean 65 mm Hg at head level), core temperature, or level of anesthetic being administered. Blood gas analysis showed an arterial P_{O_2} of 221 mm Hg and a P_{CO_2} of 28 mm Hg. The surgical team felt that the dissection being carried out at that point was too superficial to account for the loss of the cortical SSEP waveform. We considered position-related high spinal cord compression as a consequence of hyperflexion of the neck and the occurrence of paradoxical venous air embolism, but reevaluation of the patient's position did not reveal excessive flexion, nor had there been any evidence of air embolism by precordial Doppler. Rather, the close temporal relationship of the SSEP loss to dural opening, the (at least initial) absence of latency changes, and the remoteness of the ongoing surgical dissection from the monitored neural pathway led us to suspect artifact rather than injury as the cause for the SSEP change. Specifically, we suspected that the loss of the evoked response might be a recording artifact occasioned by the entry of air into the subdural or subarachnoid space. No intervention was made, and the surgery proceeded uneventfully. As soon as an airtight seal of the intracranial compartment was achieved by surgical closure, N_2O was discontinued to decrease the risk of tension pneumocephalus. A lateral skull x-ray film obtained at this time demonstrated a large accumulation of intracranial gas beneath the cortical SSEP recording electrodes (Fig. 2). Thirty minutes after elimination of N_2O from the inspired gas, with the patient still in the seated position, repeat skull films showed the persistence of a large amount of intracranial gas (Fig. 3). In the antero–posterior view, the cortical surface of the brain was separated from the recording electrodes by a gas space measuring approximately 3 cm (without allowance for magnification due to x-ray technique). SSEPs continued to show the absence of recognizable cortical waveforms with preservation of Erb's point potentials. The patient was then placed in the supine position and the headholder removed. An SSEP obtained 7 min thereafter showed cortical waveforms that closely resembled the baseline recordings (Fig. 1). Simultaneously, a lateral skull film revealed migration of intracranial gas away from the

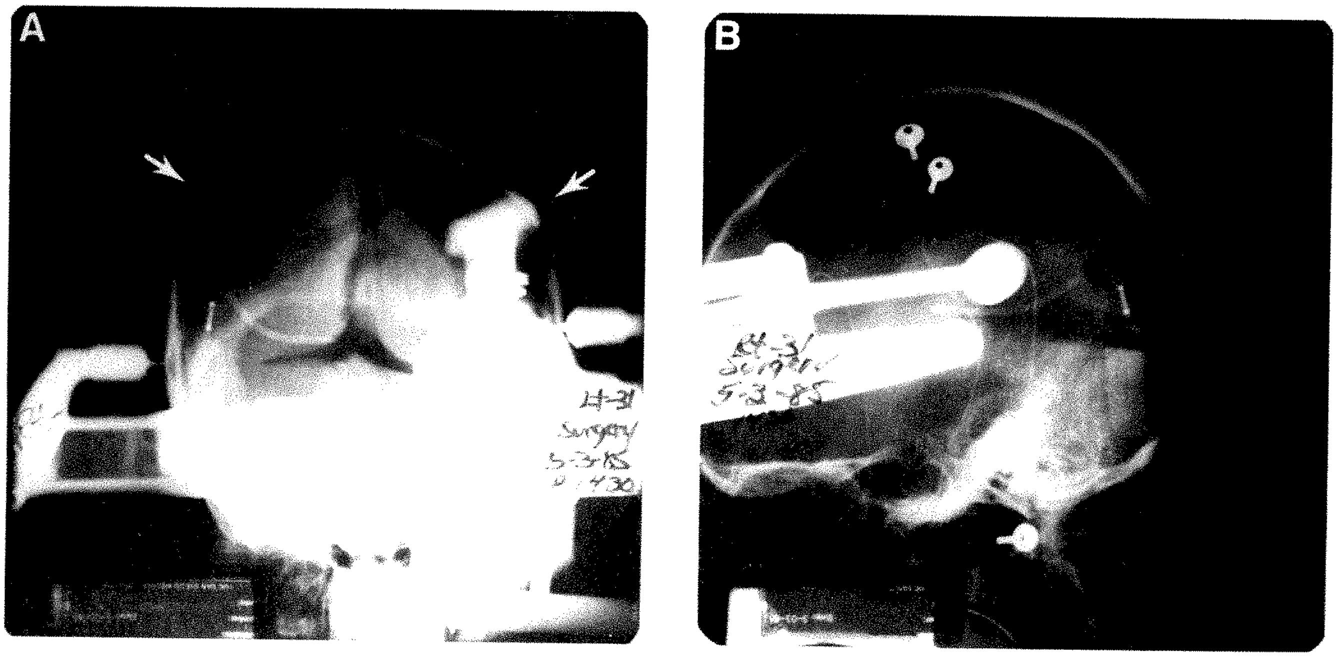

Figure 3. Antero-posterior (A) and lateral (B) skull films obtained immediately before removal of the headholder and assumption of the supine position. Note the characteristic appearance of subdural gas in A, outlining the falx and tentorium (2). Approximately 3 cm of gas separate the SSEP disk electrodes (arrows) from the cortical surface.

recording electrodes and towards the region of the frontal poles (Fig. 4). Isoflurane (0.2%) and the fentanyl infusion were discontinued. The patient awakened promptly and was extubated in the operating room where he responded appropriately to questions and commands and was free of neurologic deficit. He continued to do well and was discharged from the hospital 4 days after surgery.

Discussion

The clinical utility of evoked responses as monitors of intraoperative neural injury depends considerably on the physician's ability to distinguish nonpathologic SER changes from pathologic ones. Many factors are known to affect evoked response waveforms during surgery and anesthesia (2). These include inhalation anesthetics, narcotics, barbiturates, and other sedatives; surgical and position-related trauma to the neural pathway at risk; hypoxia, ischemia, and hypothermia; as well as a variety of technical factors including equipment malfunction and high electrode impedance.

All of these factors were reviewed and none could account for the dramatic loss of the cortical SSEP in our patient. Only then was the presumptive diagnosis of intracranial gas entertained. It seems likely that the collection of intracranial gas resulted merely in the inability to record the cortical evoked response rather than having caused injury to monitored neural pathways. The immediate return of the cortical waveform on resumption of the supine position and the fact that the patient awakened promptly without neurologic deficit speak strongly against the possibility that the evoked response changes were due to pressure-related injury produced by the pocket of intracranial gas. Furthermore, the brain was slack, and it was the opinion of the surgeons that the supratentorial space was in free communication with the atmosphere via the sudural or subarachnoid space, and that a tension phenomenon was unlikely. The absence of gas–fluid levels on x-ray further supported this opinion, indicating that little, if any cerebrospinal fluid could have been present to prevent free communication between the intracranial gas space and the atmosphere during the dissection. Therefore we suggest that the observed changes were the result of intracranial gas acting as an insulator between the neural generators of the near-field cortical potential and the recording electrodes, thus preventing the detection of the electrical signals which make up an evoked response waveform.

In summary, this report reaffirms that large amounts of intracranial gas can accumulate during craniectomy in the seated position (3–8), particularly in patients with functioning ventriculo-peritoneal shunts (9–11), and suggests that such gas pockets may interfere with the monitoring of cortical somatosensory evoked responses. Although artifactual in the sense of not having been the result of neural injury, a loss of the SSEP

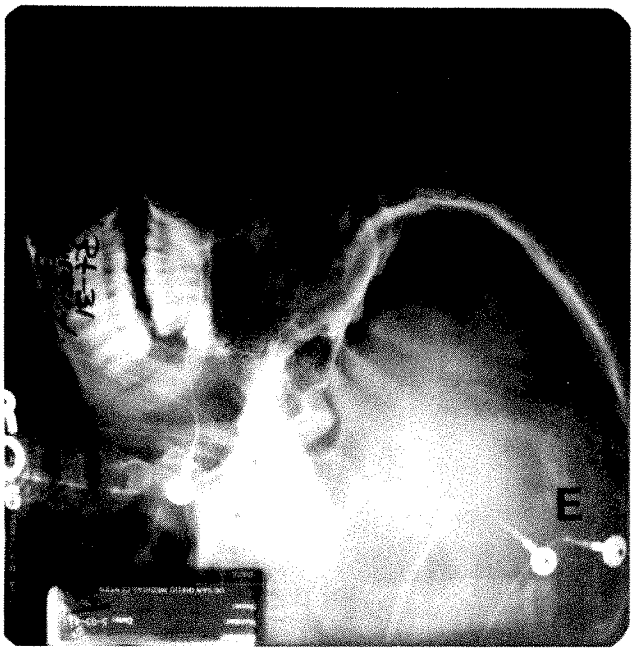

Figure 4. Lateral skull x-ray film taken 7 min after the patient had been placed in the supine position. The intracranial gas pocket is now seen in the region of the frontal poles, away from the cortical electrodes (E).

under these circumstances may nevertheless serve a useful function. It can alert the operating team, as it did in our case, to the possibility of accumulating intracranial gas. An awareness of the presence of an intracranial gas space may be relevant to interpretation and management of a "tight" brain during a craniotomy and may contribute to decisions regarding the use or omission of nitrous oxide (12–14). Knowledge of the presence of intracranial gas may also be important in the evaluation and treatment of delayed awakening following neurosurgical procedures (10).

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Note Added in Proof

Subsequent to the submission of this report, a similar event has been described (McPherson RW, Toung TJK, Johnson RM, Rosenbaum AE, Wang H. Intracranial subdural gas: a cause of false positive change of intraoperative somatosensory evoked potential. Anesthesiology 1985;62:816–9).

Hemolysis after Administration of High-Dose Fentanyl

Hitoshi Furuya, MD, and Fukuichiro Okumura, MD

Because we have encountered instances of hemolysis after administration of high-dose fentanyl, a complication not previously reported, we designed a study to clarify clinically and experimentally the causes of hemolysis after the administration of high-dose fentanyl.

Methods

To confirm the association of hemolysis and fentanyl, ten patients scheduled for coronary artery bypass graft were studied with their informed consent. None had a history of hemolytic disease. In seven patients anesthesia was induced with high dose fentanyl (0.037 mg/kg of fentanyl, 0.74 ml/kg of fentanyl citrate solution), given intravenously in 3 min, and intubation was performed after administration of 0.16 mg/kg of pancuronium bromide. Additional fentanyl (0.053 mg/kg of fentanyl, 1.06 ml/kg of fentanyl citrate solution) was given before sternotomy, approximately 20 min after induction. As the control, three patients were anesthetized by slow induction with 1–3% halothane and 50% nitrous oxide and intubated with the aid of pancuronium bromide. Heparinized blood was collected from the radial artery before induction of anesthesia, after intubation, and after sternotomy. Serum was separated from the blood by centrifugation at 1500 rpm for 5 min, and serum hemoglobin was measured by the method mentioned below.

To clarify the cause of hemolysis, an in vitro study was also performed. Ten ml of heparinized blood was collected from the median cubital veins of five volunteers. The blood was then washed by normal saline and centrifuged at 1500 rpm for 5 min to remove the buffy coat. This procedure was repeated three times, after which saline was added to prepare a solution of red blood cells in saline with a hemoglobin content of 10 g/dl. One-tenth ml of a solution containing 1.25, 2.5, or 5 μg of fentanyl with 50 μg of paraoxybenzoate methyl and 5 μg of paraoxybenzoate propyl per 0.1 ml, respectively, were added to 2.9 ml of the solution of red blood cells in saline. The concentrations of fentanyl were based upon doses used clinically. One-tenth ml of normal saline was also added to the red blood cell solution as a control. The solutions were then incubated for 10 min at 37°C and centrifuged at 1500 rpm for 5 min. Hemoglobin concentration of the supernatant was measured at 630 nm with a spectrophotometer by the benzidine method, and the osmotic pressure of the supernatant was measured by Fiske's osmometer. Two ml of the commercial fentanyl contains 0.1 mg of fentanyl, 1 mg of paraoxybenzoate methyl, and 0.1 mg of paraoxybenzoate propyl as preservative. Statistical analysis was performed by Student's *t*-test, and *P* values of less than 0.05 were considered significant.

Results

In the clinical study serum-free hemoglobin levels of patients given high-dose fentanyl increased in proportion to doses of fentanyl administered, and there was no increase of serum-free hemoglobin in patients anesthetized with halothane. Mean serum-free hemoglobin values in mg/dl were 1.6 before induction, 7.8 after intubation, and 14.3 after sternotomy in the high-dose fentanyl group. The highest value, 26.2 mg/dl, was obtained after sternotomy (Fig. 1, Table 1).

For the in vitro study, mean hemoglobin levels of the supernatant of the mixture are shown in Table 2. Compared to the control, the experimental group showed no significant increase in hemoglobin concentration of the supernatant with fentanyl or preservatives. Osmotic pressures of the mixture were significantly lower than with saline, although still within the normal range. The osmotic pressure of commercial fentanyl solution is 10 mOsm/L.

Discussion

In our clinical study, free hemoglobin levels in serum increased in patients given high doses of fentanyl but not in patients given halothane, indicating hemolysis was due to administration of high-dose fentanyl and

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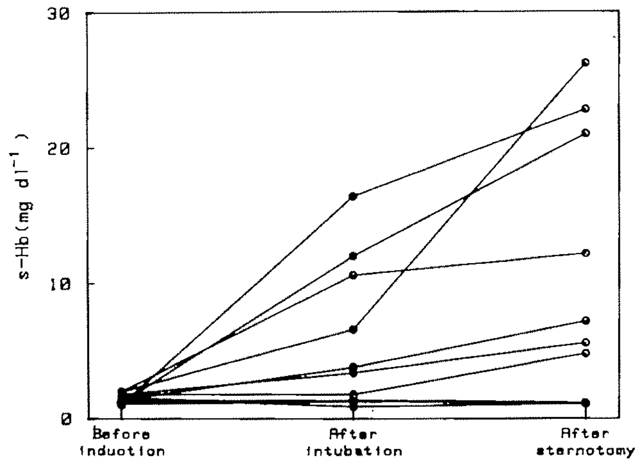

Figure 1. Serum hemoglobin concentrations in patients anesthetized with high dose fentanyl (open circles) and with halothane (closed circles).

Table 1. Free Hemoglobin Concentrations in Serum of Patients Given High-Dose Fentanyl or Halothane

	Before induction	After intubation	After sternotomy
High-dose fentanyl group (mg/dl)(n = 7)	1.6 ± 0.4	7.8 ± 5.4	14.3 ± 8.9
Halothane group (mg/dl)(n = 3)	1.3 ± 0.2^a	1.3 ± 0.3^a	1.1 ± 0^b

High-dose fentanyl group vs halothane group.
^{a}Not significant. ^{b}$P < 0.05$.

Table 2. Hemoglobin Concentration and Osmotic Pressure of the Supernatant of Mixtures Studied in In Vitro Experiments

Solution tested (ml)	Hb (mg/dl); mean ± SD (n = 5)	Osmotic pressure of the supernatant (mOsm/L); mean ± SD (n = 5)
Saline 0.1 (control)	8.9 ± 5.5	294.6 ± 1.5
Distilled water 0.1	11.6 ± 4.7^a	281.2 ± 2.0^b
Fentanyl 0.1	8.4 ± 3.5^a	281.6 ± 0.9^b
Fentanyl 0.05 + distilled water 0.05	11.5 ± 2.5^a	283.4 ± 3.0^b
Fentanyl 0.025 + distilled water 0.075	11.1 ± 2.5^a	284.0 ± 4.1^b
Preservatives 0.1	10.4 ± 1.8^a	281.3 ± 1.3^b
Commercial fentanyl solution	—	10

See text for details. No significant differences in free hemoglobin levels with saline and with fentanyl or preservatives.

not to the surgery performed. In the in vitro study, neither fentanyl itself nor its preservatives caused hemolysis, at least in clinically effective concentrations, and the osmotic pressures of the mixtures were not sufficiently changed to cause hemolysis. The most likely reason for hemolysis associated with high-dose fentanyl anesthesia under clinical conditions thus appears to be rapid administration of a large volume of hypotonic fentanyl solution into a peripheral vein with resulting hypotonic hemolysis. Large volumes of fentanyl therefore should be injected slowly or administered after being mixed with an isotonic fluid, even though the clinical significance of the hemolysis we observed remains to be defined.

Letters to the Editor

Malignant Hyperthermia Diathesis and Sudden Infant Death Syndrome

To the Editor:

Denborough and colleagues reported in 1982 that among 50 families of sudden infant death syndrome (SIDS) victims queried, 13 had a history of anesthetic deaths or serious reactions to anesthetics, myopathy, or multiple SIDS (1). Muscle biopsy specimens were obtained during elective surgery from 15 parents of 13 SIDS victims from families with a positive family history. Five of the 15 exhibited increased muscle contractility when tested for sensitivity to halothane and caffeine. They concluded that an acute disorder of myoplasmic calcium metabolism may be responsible for some sudden infant deaths.

To determine whether the family medical histories were unique to SIDS families, we used a specially designed and pretested survey form to query 51 SIDS families and 97 non-SIDS families matched on number of live born children so that risk of SIDS would be comparable. The form contained questions unrelated to the hypothesis to disguise the purpose of the survey.

Fourteen of the 51 SIDS families (27.5%) had a positive family history as described by Denborough, compared with five of the 97 non-SIDS families (5.2%). The difference in proportions is statistically significant ($\chi^2 = 14.84$, $P < 0.001$). There was no statistical difference in responses to questions intended to disguise the purpose of the survey, i.e., heat exhaustion, fever reaction to medicine, twins, floppy baby diagnosis, cerebral palsy, infantile apnea. All positive responses, regardless of the question, were about equally divided between maternal and paternal lineages.

This study not only confirms the medical history association reported by Denborough et al. but also indicates it is relatively unique to SIDS families, and thus may warrant further investigation.

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Reference

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A Method For Securing "Piggyback" Infusions[1]

To the Editor:

Surgical patients may require intraoperative infusions of vasopressor or vasodilator solutions either alone or together. Placement of the intravenous tubing drug infusions near the intravenous catheter hub minimizes tubing dead space that contributes to delay in onset and the overshoot of the desired effects.

It is our practice to place in line, at the intravenous catheter hub, infusions of vasopressor or vasodilator solutions for all patients undergoing carotid endarterectomy. Optimal surgical exposure requires the patients' arms to be padded and tucked by their sides. Thus access to their intravenous sites during surgery is difficult, and a secure method for placing these infusions is necessary. Needles placed in the injection ports of the patient intravenous tubing prove unsatisfactory because they may become disconnected and may lacerate the tubing. Three-way stopcocks are bulky and may become entangled and disconnected during padding and positioning of the arms. They are difficult to manipulate under the drapes and are associated with a large amount of pharmacologic dead space between the stop-cock and the intravenous catheter.

A simple, economical solution to this problem was reached by modifying an "extension set with T-piece" (Abbott Hospitals, Inc., Product # 4612) that we routinely stock for pediatric intravenous sets (Fig. 1). The rubber injection port is removed. The plastic T is placed in line between the patient's intravenous tubing and the intravenous catheter hub. The short length of tubing is then connected to the drug infusion. The infusions are administered by infusion pump to prevent reflux of maintenance intravenous fluid into the drug infusion tubing and to provide precise control of drug dosages. This makes a compact, flexible, secure means for administering drug infusions that has minimal propensity for disconnection. Furthermore, T-pieces may be placed in series and used to provide simultaneous infusions such as inotropes and vasodilators in critically ill patients.

This arrangement is used for all carotid artery surgery and has been adapted to other procedures. It is a simple,

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[1] The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of Defense or the Department of the Army or as endorsing any commercial product or manufacturer.

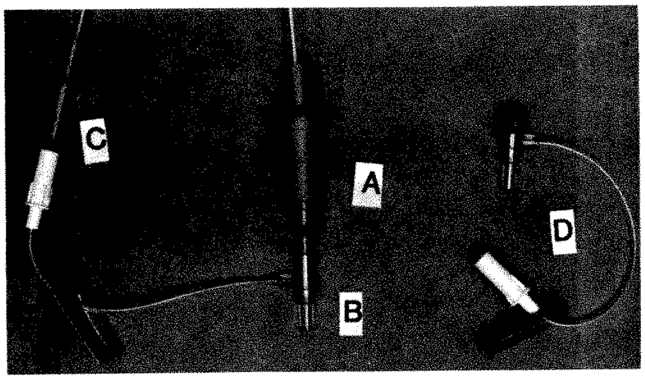

Figure 1. A, Patient IV tubing; B, T-piece in line ready for connection to IV catheter; C, drug infusion tubing; D, extension set with T-piece before modification by removal of rubber injection port.

economical modification of an item that is already available in many anesthesia workrooms.

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Cholinergic Dysfunction and the Anesthetic State

To the Editor:

The fact that anesthetic agents interfere with various central nervous system transmitter mechanisms has become common professional knowledge (1). It is therefore not surprising that halothane modifies the functioning of the central cholinergic system as reported by Johnson and Hartzell (2). We fail, however, to understand why these two investigators decided to discuss the mechanism (unitary or nonunitary) of the anesthetized state on the basis of their results.

On the first major flaw of their study we agree completely with J.R. Trudell's editorial (3). The omission of testing the studied halothane concentrations in vivo against a functioning CNS-cholinergic system (e.g., by providing continuous administration of physostigmine) forms the second major objection to the implications drawn from their study. We feel that it is misleading to assume that a dysfunction of the CNS-cholinergic system contributes significantly to the production of general anesthesia. We are quite aware of the fact that excessive doses of an anticholinergic agent may produce a comatose patient. However, any of the centrally active drugs in excess may produce coma, yet we do not dub them "anesthetic agents." Furthermore, we have shown that central cholinergic blockade is not essential for the anesthetic state in a repeated clinical study with different inhalation and intravenous anesthetic agents (4).

Instead of piling one more stone on the wall of confusion that obscures the mechanism of anesthesia (3), the results of Johnson and Hartzell's study could have contributed to understanding better the recovery from anesthesia. The authors should have discussed their data in the light of the fact that most inhalational anesthetics produce some CNS-cholinergic blockade, which manifests itself as the central anticholinergic syndrome during recovery (1).

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Acid Aspiration Risk Factors

To the Editor:

We wish to draw attention to an apparent discrepancy in the paper entitled "Assessment of Age-related Acid Aspiration Risk Factors in Pediatric, Adult, and Geriatric Patients" (Manchikanti L, Colliver JA, Marrero TC, Roush JR. Anesth Analg 1985;64:11-7). In the abstract, the results, and the discussion they report a correlation between duration of fast and gastric acidity, with the specific comment on page 14 that "as length of fasting period increased, pH decreased." Figure 3, which illustrates their data on this relationship, clearly shows, however, that as duration of fasting period increased, pH *increased*! This finding (that a longer fast results in more alkaline gastric contents) is in agreement with a study of our own which is presently in preparation.

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In Response:

We thank Drs. Hutchinson and Merry for noting the error in our description of the relationship between length of fasting period and gastric pH depicted in Figure 3 of our article. As Drs. Hutchinson and Merry correctly note, the results show that pH increased as length of fasting period increased. We sincerely regret the error.

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Nuffield Department of Anaesthetics, Oxford

A Scientific Meeting will be held in Oxford from July 23–25, 1987, to celebrate the Fiftieth Anniversary of the founding of the Nuffield Department of Anaesthetics. This meeting will follow the Second World Congress on the History of Anaesthesia, which is to be held in London from July 20–23, 1987.

Anaesthetists and others who have had connections with the Department are invited to write to the Nuffield Department of Anaesthetics, (Dept. GP/87), Radcliffe Infirmary, Woodstock Road, Oxford, OX2 6HE, England, enclosing their full name and postal address so that they may be provided with further particulars.

Professor M.K. Sykes
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Atracurium and Pheochromocytoma

To the Editor:

I was most interested in the report by Stirt et al. (1) of the use of atracurium in a patient with a pheochromocytoma because of my different experience in a similar situation.

A 31-yr-old man with a left adrenal pheochromocytoma was prepared for operation with phenoxybenzamine, 20 mg, twice daily, metoprolol, 100 mg, twice daily and chlorpromazine, 25 mg. One hr after receiving intramuscular papaveretum, 20 mg, and hyoscine, 400 μg, he arrived in the induction room with an arterial blood pressure of 130/88 mm Hg and a heart rate of 78 beats/min. Deep sedation was achieved with intravenous diazemuls, 10 mg, and fentanyl, 100 μg, while a radial artery catheter was inserted. Anesthesia was induced with intravenous thiopental, 400 mg, followed by atracurium, 30 mg, and manual ventilation of the lungs with nitrous oxide, 50%, in oxygen and enflurane, 1%. The arterial blood pressure increased immediately and progressively to 200/120 mm Hg while ventricular bigeminy occurred. Control of both this hypertension and the arrhythmia was achieved with intravenous practolol, 5 mg. Tracheal intubation followed, and the blood pressure returned to normal levels, remaining stable thereafter, apart from one reading of 166/110 mm Hg during initial exploration of the tumor.

We used vecuronium in a subsequent patient and, like Gencarelli et al. (2), were impressed by the stability of the blood pressure. Vecuronium may be preferable because atracurium releases histamine (3).

The excellent control of the arterial blood pressure achieved by Dr. Stirt et al. in their patient is, perhaps, a tribute to deep anesthesia compared to deep sedation and light anesthesia. The experienced French workers Desmonts and Marty (4) also have emphasized the value of deep anesthesia in preventing hypertension during induction in these patients.

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Oxygen Flowmeter Failure on the North American Dräger Narkomed 2a Anesthesia Machine

To the Editor:

We report an oxygen flowmeter failure on a Narkomed 2a anesthesia machine. Our problem developed as oxygen flow was interrupted during endotracheal intubation. When we attempted to reestablish flow, the oxygen flowmeter control knob firmly stopped after opening only about 1/8 of a revolution. This produced less than 200 ml/min of oxygen flow, inadequate for patient ventilation. A parallel air flowmeter was used to supply air with which to ventilate the patient.

The NA Dräger Narkomed 2a and other Dräger machines utilize two pins to effect a stop mechanism for flowmeter control knobs. One pin is set into the back of the control knob projecting toward the machine. The other is set into the machine and projects toward the control knob (Fig. 1). The pins engage each other and prevent further knob rotation when the needle valve stem just seats in its orifice. This stop mechanism prevents the needle tip from overturning into the seat and prevents damage to the valve. When the flowmeter valve is opened, the knob and its pin move away from the machine with each revolution. The knob is adjusted on the stem so that the pins just clear after one opening revolution and separate further with subsequent turns.

The failure occurred when the knob was turned clockwise, past the off position where the pins usually engage. Closure was presumably stopped by impaction of the valve stem in the seat. When we attempted to reopen the valve, the pins engaged in a reversed relationship, preventing further rotation and full flow.

Our flowmeter was eventually unstuck by applying traction to the knob as the valve was opened. Repair was ef-

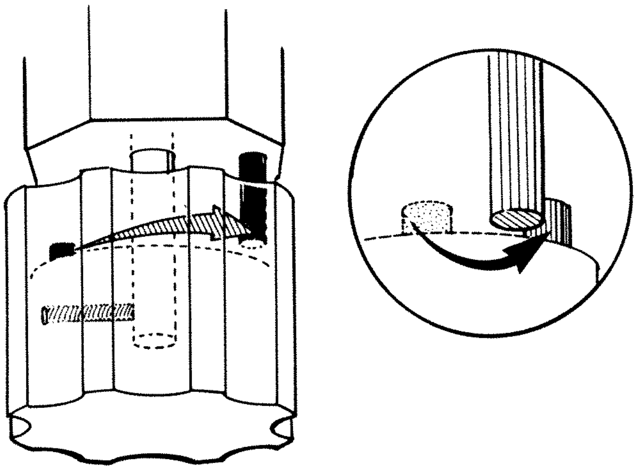

Figure 1. The orientation of the pins that effect a stop mechanism is illustrated. Inset demonstrates how the valve locked closed.

fected by repositioning the knob on the valve shaft. This mechanism of flowmeter failure and its resolution should be known by all who use NA Dräger anesthesia machines.

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Vecuronium and Malignant Hyperthermia

To the Editor:

The conclusions drawn by Buzello et al (1) regarding the nontriggering characteristics of vecuronium in malignant hyperthermia (MH) susceptible pigs is disturbing. It may be true that vecuronium, like pancuronium, is a nontriggering agent, but this study does not suppport that conclusion.

The most significant results are those of pig 1. The authors blame 3 hr of surgical stimulation for triggering this pig, because its temperature increased 1.9°C over the 3 hr. However, at the end of surgery there was no tachycardia, and the end-tidal CO_2 (ET_{CO_2}) and mixed-venous oxygen ($S\bar{v}_{O_2}$) were normal. Then, after only 22 min of the vecuronium infusion, the heart rate rose to 263 beats/min, the temperature increased to 44.9°C, the ET_{CO_2} increased from 23 to 102 torr, and the $S\bar{v}_{O_2}$ decreased from 96 to 23%. It would seem that this pig triggered during those 22 min, and not during surgery.

Pig 1 may have been the most MH-susceptible of the eight; because the pigs were from an outbred colony, their spectrum of susceptibility would be quite broad. Perhaps this is why only one of eight pigs triggered on exposure to vecuronium, especially if it is only a weak trigger of MH. The fact that pig 1 had been exposed to vecuronium on two previous occasions without incident is irrelevant. Pig 1 may not have been as susceptible as an inbred MH-susceptible pig and would not consistently trigger on exposure to a triggering agent. There is a case of a human MH-susceptible patient who triggered on his thirteenth anesthetic exposure (2).

Is it possible that vecuronium potentiates the triggering effect of halothane? Two of the other seven pigs (numbers 5 and 8) triggered after only 4 min of exposure to halothane. The authors do not mention how susceptible these two pigs were on their initial halothane screening tests. Perhaps the exposure time to halothane is decreased in the presence of vecuronium, making vecuronium a weak trigger of MH.

The authors describe their pigs as coming from an outbred colony and refer to an abstract they published in 1984. The abstract states that the tested pigs were from an inbred colony. This discrepancy needs to be clarified in light of the results. Also, the authors refer to "the surgical procedure" without giving details. The procedure or procedures (if different for each pig) done also could affect the results.

In conclusion, the results speak for themselves. One pig out of a group of eight MH-susceptible outbred pigs triggered on exposure to vecuronium. The authors' explanations for this are questionable because they do not fit the results as presented. Vecuronium may be safe in MH-susceptible pigs and patients, but this paper does not prove this.

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Prolonged QT Interval Syndromes

To the Editor:

In their review of prolonged QT interval syndromes, Drs. Galloway and Glass discuss that the most accepted theory of the congenital form results from an asymmetrical adrenergic stimulus in the heart and that the drugs of first choice are β-adrenergic blockers (1). Because adrenergic stimuli are best avoided in these patients, perhaps the β-adrenergic blocking drugs pindolol and oxprenolol should not be used because of their intrinsic sympathomimetic activity (2).

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In Response:

Dr. Cervenko makes an interesting comment that β-adrenergic blocking drugs with intrinsic sympathomimetic activity (ISA) should be contraindicated in patients with the congenital form of the prolonged QT interval syndrome (LQTS). This, however, is not necessarily so. Schwartz et al., in a review of the treatment of LQTS, list numerous patients who have been successfully treated with either pindolol, oxprenolol, or practolol. All three of these β-adrenergic blocking drugs have ISA. There are several reasons why β-blocking drugs with ISA are not necessarily contraindicated in LQTS. β-Blockers with ISA allow for more complete β-adrenergic blockade of the patient. Complete β-adrenergic blockade is important when treating patients with LQTS. The exact mechanism by which β-adrenergic blockers possess ISA is not completely understood and is not necessarily due to direct adrenergic stimulation of the heart. Therefore this mechanism may not play a significant role in patients with LQTS. Both of the two β-adrenergic blockers mentioned by Dr. Cervenko, pindolol and oxprenolol (the latter is not available in the US), have membrane stabilizing activity. Several of the other drugs (phenobarbital, primidone, and phenytoin) used in the treatment of LQTS also have membrane stabilizing activity. It is still not certain whether all these drugs prevent dysrhythmias in the LQTS by their membrane stabilizing property, rather than by their other actions. It would therefore appear that complete β-adrenergic blockade with any β-blocker is the most important determinant of successful treatment with β-adrenergic drugs in the LQTS.

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A New Technique for Stabilizing the Oxygen Saturation Monitor Probe in Infants and Children

To the Editor:

The development of the oxygen saturation monitor has been a significant advance in the monitoring of infants and small children, both during anesthesia and in the intensive care unit. However, it has been difficult to maintain the position of the oximeter probe without movement on the foot or hand of an infant or small child. In addition, the warming lights that are frequently used in such situations significantly affect the apparatus so that accurate measurements cannot be obtained. We have recently started to wrap the limb with the readily available Webril gauze that is used for cushioning plaster casts. The Webril serves two purposes: it fixes the position of the oximeter probe on the extremity so there is no movement during surgery and operation of the monitor, and the light is also kept off of the probe, thereby preventing interference with the pulse trace and oxygen saturation reading. Although this may seem to be a trivial problem, failure to prevent movement of the oximeter probe may be the cause of much unwarrented anxiety when employing this useful monitoring tool. We hope that this technique will prove to be helpful to our colleagues.

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Book Reviews

Acute Respiratory Failure

W. M. Zapol and K. J. Falke, eds. New York: Marcel Dekker, Inc., 1985, 674 pp, $99.75.

This is an excellent book and the 24th volume in the continuing series, "Lung Biology in Health and Disease." It should be high on a list of priority reading for those individuals—clinicians or basic scientists—with an interest in acute respiratory failure in general and the adult respiratory distress syndrome (ARDS) in particular. The authors represent an international assemblage, all of whom are superbly qualified to write about their particular subjects. Topics include etiology, morphologic changes, fluid and electrolyte transport in the injured lung, mediators of lung injury, infection, oxygen transfer, cardiopulmonary interaction, and renal function in ARDS. Although clinical subjects are covered, particularly with respect to altered respiratory mechanics, airway pressure therapy, cardiac function, and renal dysfunction, the emphasis is clearly on the pathogenesis and the pathophysiology of ARDS. Those interested primarily only in an overview of therapeutic interventions need to look elsewhere.

The editors' personal biases are apparent in their emphasis on pulmonary vascular changes. Three chapters (2, 6, and 7) devote 180 pages out of the total 641 to various aspects of this subject. Major interest in pulmonary hypertension and ARDS has been a fact of life at the Massachusetts General Hospital for many years. Although the accuracy of statements such as, "The pulmonary artery pressure is always elevated in ARDS . . ." may be questioned (few things in medicine or anything else always happen), the topic, nevertheless, is important and generally well done. Pulmonary angiograms and electron photomicrographs are numerous, of excellent quality, and clearly demonstrate the pathological features of interest.

The strength of this text lies in its treatment of the mediators known or suspected to be at least in part responsible for ARDS. For many years we have understood in general terms what happened to patients with this syndrome, but we have not known why. The past few years have provided a tremendous outpouring of work concerning the genesis of ARDS and the roles of leukoembolization and agglutination within the pulmonary circulation, complement activation, alterations in coagulation mechanisms and fibrin deposition, toxic oxygen radicals, and a host of biologically active peptides. These areas are discussed comprehensively and represent the best summary of current knowledge I have seen. A chapter on the potential prevention of end-stage fibrosis, "the final pathway" in refractory ARDS, is of particular interest for future therapy.

This book succeeds in providing the up-to-date approach to ARDS described by Dr. Claude Lenfant in his introduction. References are pertinent and recent. The major contributions of individuals from "The General" are included in a moving tribute to Myron B ("Mike") Laver written by Dr. Henrik Bendixen. Few readers will be disappointed. Most will find the text a valuable addition to their knowledge of an incredibly complex field.

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Acute Pain

G. Smith and B. G. Covino, eds. Stoneham, MA: Butterworths, 1985, 270 pp, $59.95.

Anesthesiologists' interest in the subject of acute pain therapy is a natural outgrowth of their management of postoperative pain in the recovery room. Curiously, however, most pain clinics—even those run by anesthesiologists—are concerned more with chronic than acute pain, and the current pain literature reflects this bias. The editors of this book have attempted to fill this void by providing a book which would be "of benefit not only to anesthesiologists and surgeons, but also rheumatologists, traumatologists, family practitioners and all other medical disciplines which are required to treat acute, severe, pain."

This work, however, falls far short of that ideal. At 270 pages, it is too short to adequately discuss such a comprehensive subject. This brevity is reflected in the inadequacy of many of the chapters. Renal colic, for example, is a not uncommon acute pain problem, yet this subject receives only 9 lines of print with no references. Pancreatitis is mentioned with almost equal brevity.

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The chapter on pharmacokinetics is a thorough and learned discussion of the pharmacology of parenteral drug administration, though one wonders if the average reader would be truly interested in "use of statistical moment theory for pharmacokinetic analysis . . . ." This chapter is also lacking in any summary or list of general principles that could be applied to clinical practice.

The use of American and British authors creates some cultural problems: the otherwise excellent chapter by Chris Hull devotes 9 of 21 pages to a discussion of patient-controlled analgesia but fails to mention the 2 devices commercially available in the US.

Roughly half the book is devoted to the physiology, pharmacology, and psychology of pain. In most cases, these authors fail to distinguish between acute, chronic, cancer, and experimental pain. One might also question the amount of space given to the basic science of pain given the rather incomplete and inadequate discussions of clinical applications that follow.

As with any multiauthored text, the quality is variable, and subjects are sometimes repeated. The pharmacology of narcotics, for example, is repeated at least twice. Hypnosis is discussed twice in the same chapter.

The quality of the publication is not exceptional. In the copy sent to me by the publisher, the end papers were folded and glued to the title page.

The biggest drawback to this book, however, is its price. At $59.95 it seems designed more to enrich the editors than the medical literature. The quality of the material is not commensurate with the reputations of the authors, and it is doubtful if this book would be of interest to the serious student of pain. The authors state in their preface that "there is no text providing a comprehensive treatment of acute pain." There still is not.

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High-Frequency Ventilation in Intensive Care and During Surgery

G. C. Carlon and W. S. Howland. New York: Marcel Dekker, Inc., 1985, 297 pp, $59.75 (US and Canada), $71.50 (all other countries).

This compact volume is intended by the editors to bring together all of the pertinent current information on high frequency ventilation. To achieve this objective, the contributions of 28 authors have been organized into a logical sequence. Appropriately, the bulk of the information presented concerns high frequency jet ventilation, the modality which is most widely used, and for which there is available commercially produced equipment. The other forms of high frequency ventilation—high frequency positive pressure ventilation and high frequency oscillatory ventilation—are reviewed in sufficient depth, consistent with their current role in clinical practice.

Care is apparent in the production of this book, in that illustrations and graphics are reasonably consistent in appearance and identification throughout. Although one may expect repetition when many authors prepare their contributions without specific knowledge of the style and content of the other contributors, the editors have avoided tedious overlapping in the chapters. There is more than an acceptable minimum of typographic errors, however, although only a few are significant enough to obscure the authors' meanings.

Despite the limitation suggested by the mention of intensive care and surgery in the title, a substantial portion of the material has to do with laboratory investigation. Chapter 11, on the theoretical evaluation of high frequency ventilation, may cause eye glaze in those clinicians who persist for the entire 25 pages.

All in all, this is a worthwhile effort to bring what is known and what is currently being practiced in the area of high ventilation together in one volume.

E. Paul Didier
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The Resident's Friend

B. I. Rose. Sunnyvale, CA: Byte-Omega, 1984, $99.00.

House officers and medical students spend hours performing secretarial tasks. Residents in the Obstetrics Department at Stanford University have been using a program called *The Resident's Friend* on an Apple II computer to help document their surgical procedures, as required by many specialty boards, and to help organize patient care. The program's distributor, who purports "better patient care through computing," is hoping the software will find applications beyond obstetrics.

The software maintains three files: a patient file, a follow-up file, and a procedure file. The patient file, which is divided into active patients and discharged patients, contains the patient's name, chart number, room number, date of admission, and three free text fields. The only reports that can be generated from this file are a "Census List," organized by date entered into the computer, and a "Sign Out List," organized by room number. The follow-up file consists of the patient's name, chart number, date, two alphanumeric free text fields, and uses the patient file only to search for patient's names after entry of the first few letters. The only report available is a "Patient Follow-Up List," a simple linear file listing. The procedure file records each procedure performed, listing the patient's name, chart number, procedure, date of procedure, hospital code, level of resident's responsibility in the procedure, patient's age, and a comment. The computer can generate a list of all procedures performed, organized by date entered or by procedure and also can summarize the number of procedures by level of responsibility.

The Resident's Friend is fairly unfriendly. Disk access is quite slow, suggesting the use of linear searches rather than indexes for file access. There is little sorting of the data; files are printed on a first-in, first-out basis. Data entry appears to be accomplished with BASIC "INPUT" statements, which is well below current software standards. There is no checking for duplicate keys; if a patient or procedure is entered several times, duplicate records will be created. Because the software has been in use for two years, I was surprised to find eight bugs, several fatal, in my first hour of use.

The Resident's Friend could maintain an anesthesiology resident's list of patients and procedures in a typed and attractive format. However, it currently takes about two minutes each day to maintain my patient list and about two hours at the end of the year to summarize it. *The Resident's Friend* would take about fifteen minutes each day, and I would still spend two hours at the end of the year because the program cannot give monthly subtotals. I see no use for the system by anesthesiology house officers.

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Regional Anesthesia and Clinical Applications

H. Carron, G. A. Korbon, and J. C. Rowlingson.
Orlando, FL: Grune and Stratton, 1985, 198 pp, $39.50.

This short treatise is divided into six sections that briefly cover pharmacology, spinal and epidural anesthesia, and various autonomic and somatic nerve blocks. The major attributes of the book are that it is concise and contains 110 illustrations that are generally excellent. Unfortunately the attempt to be concise results in a book that is sometimes sketchy and arbitrary. For example, in the chapter, "Spinal and Epidural Anesthesia," the author indicates that dosage depends on many factors but does not state the factors. Rather a few arbitrary drug doses are recommended, and no reference is provided for the reader who desires a more comprehensive discussion. In fact, specific references are not supplied for any of the material. Instead a suggested reading list is provided at the end of the book.

The omission of specific references is particularly unfortunate because many of the authors' statements are controversial. For example the authors state that long-acting local anesthetics and epinephrine should not be used for stellate ganglion block. Yet the use of long-acting agents with epinephrine for stellate ganglion block is described in a number of texts (e.g., Moore, Regional Anesthesia). In addition, the authors frequently describe only their preferred techniques without acknowledging the fact that well-established, alternate techniques exist. Thus, in describing hernia block, the authors ignore classic techniques described by Moore and by Labat. Similarly, in describing coeliac plexus block, though the authors concede that most anesthesiologists perform bilateral blocks, they fail to refer to the classic technique described by Bridenbaugh and Moore. Again no reference is supplied to support the author's contention that unilateral block is usually satisfactory.

Despite the omissions, the book presents a reasonably good overview of regional anesthesia and provides adequate descriptions of the technical aspects of many useful nerve blocks. As such the book will be valuable as an introduction to regional anesthesia for medical students and for physicians who perform the occasional nerve block. Anesthesiologists and other physicians who are actively involved in teaching or performing regional anesthesia will need to refer to more comprehensive texts available on the subject.

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List of Books Received

Receipt of the following books is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Anaesthesia, Essays on its History. J. Repreht, M.J. van Lieburg, J.A. Lee, W. Erdmann. New York: Springer-Verlag, 1985, 409 pp, $49.00.

Anesthesia and Coronary Artery Surgery. S.A. Tarhan, ed. Chicago: Yearbook Medical Publishers, 381 pp, $72.70.

Atlas of Regional Anesthesia. J. Katz. Norwalk, CT: Appleton-Century-Crofts, 1985, 203 pp, $75.00.

Classical Anesthesia Files. D.M. Little JR, ed. Park Ridge, IL: Wood Library Museum, ASA, 1985, 335 pp, $35.00.

Clinical Application of Respiratory Care, 3rd edition. B.A. Shapiro, R.A. Harrison, R.M. Kacmureli, R.D. Cane, eds. Chicago: Yearbook Medical Publishers, 1985, 613 pp, $34.95.

Decision Making in Critical Care. H. Don, ed. St. Louis: CV Mosby, 1985, 205 pp, $44.00.

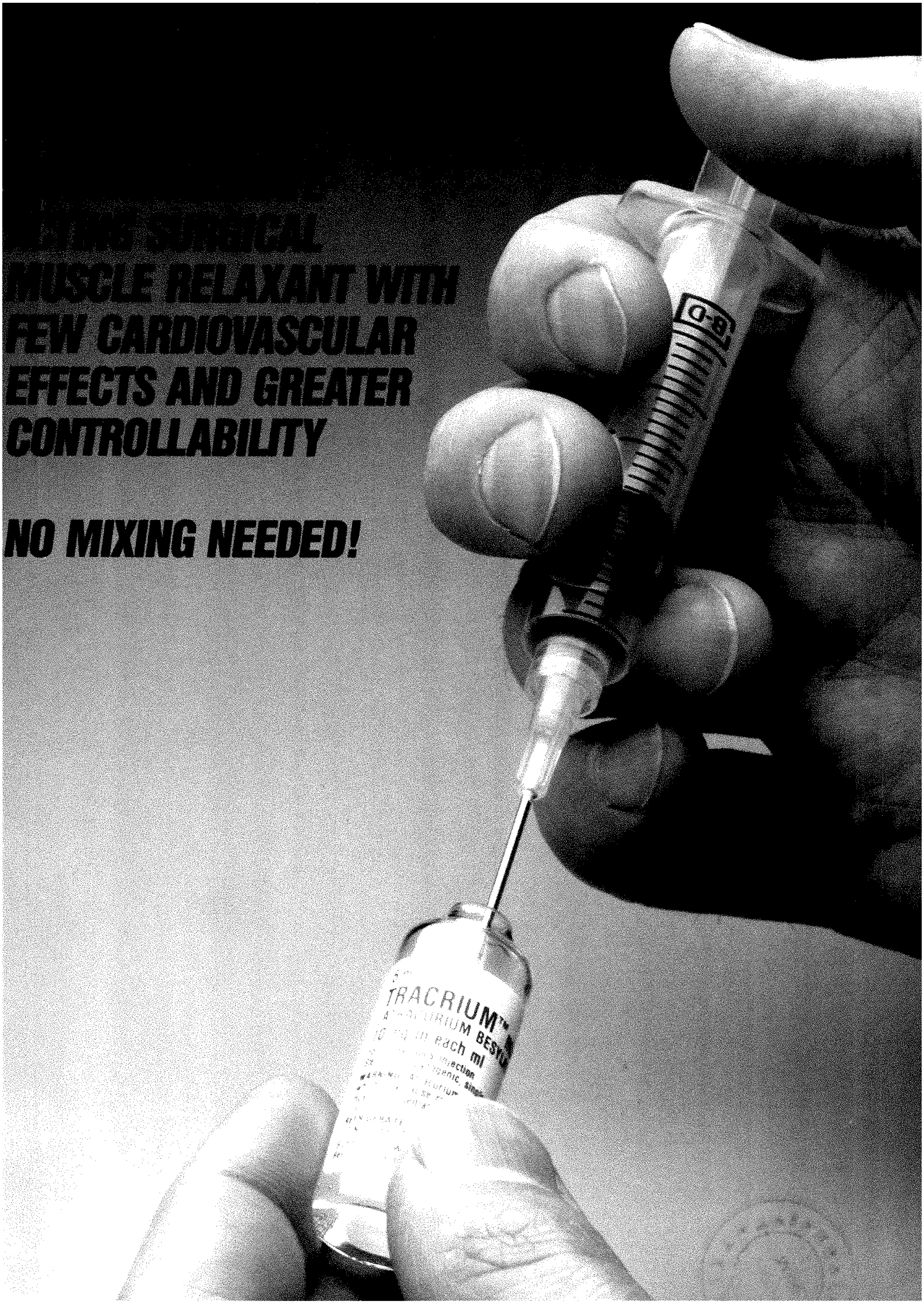
Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th edition. A.G. Gilman, L.S. Goodman, T.W. Rall, F. Murad, eds. New York: MacMillan, 1985, 1837 pp, $65.00

Handbook of Adverse Drug Reactions. M.A. Rizack, C.D.M. Hillman. New Rochelle, NY: The Medical Letter, 1985, 121 pp. $9.95.

Toxicology of Inhaled Materials. H.P. Witsche, J.D. Prain, eds. New York: Springer-Verlag, 1985, 553 pp, $172.00

1985 Yearbook of Anesthesia. R.D. Miller, R.R. Kirby, G.W. Ostheimer, L.J. Saidman, R.K. Stoelting. Chicago: Yearbook Medical Publishers, 1985, 395 pp, $42.95

1985 Yearbook of Critical Care Medicine. M. Rogers et al. Chicago: Yearbook Medical Publishers, 1985, $42.95.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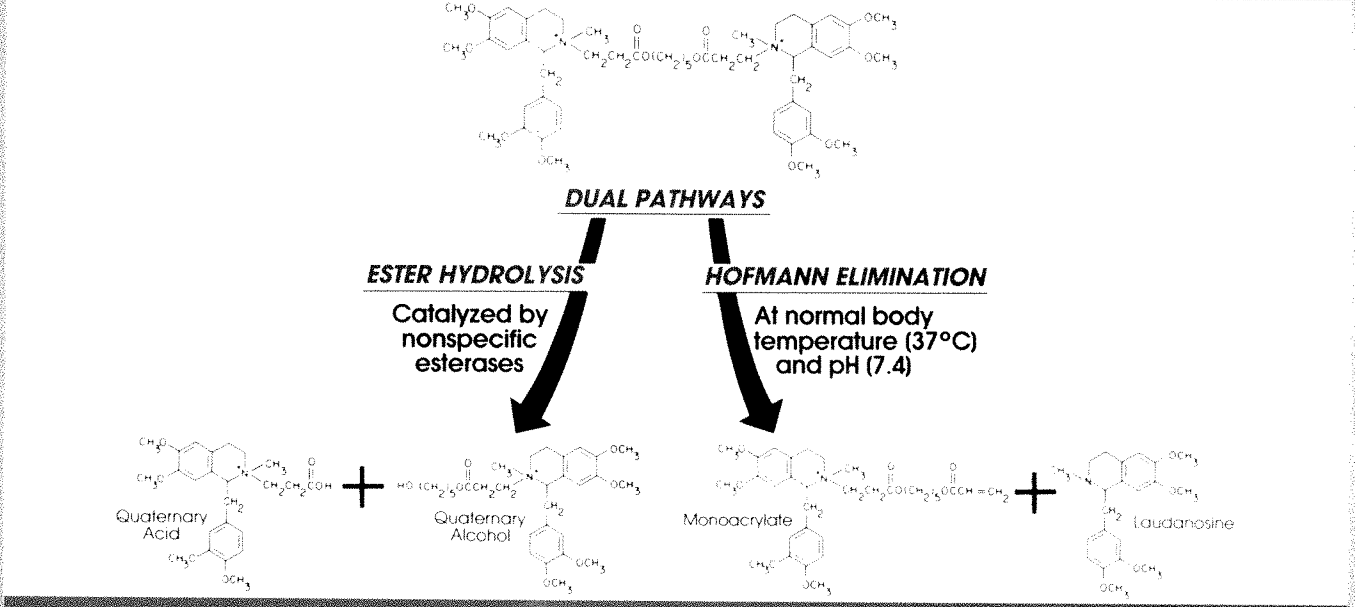


☐ *Tracrium* Injection (atracurium besylate) is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:*

1 *Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH*

2 *Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required*

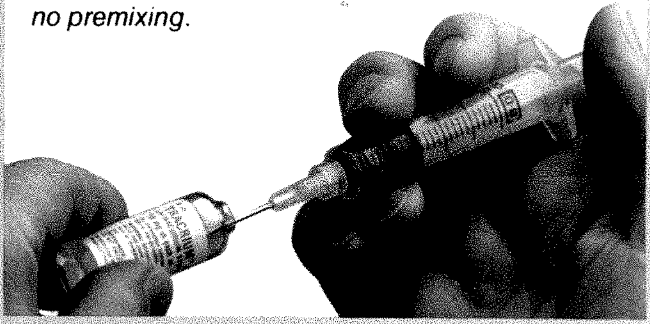
These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."[1]

"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."[2]

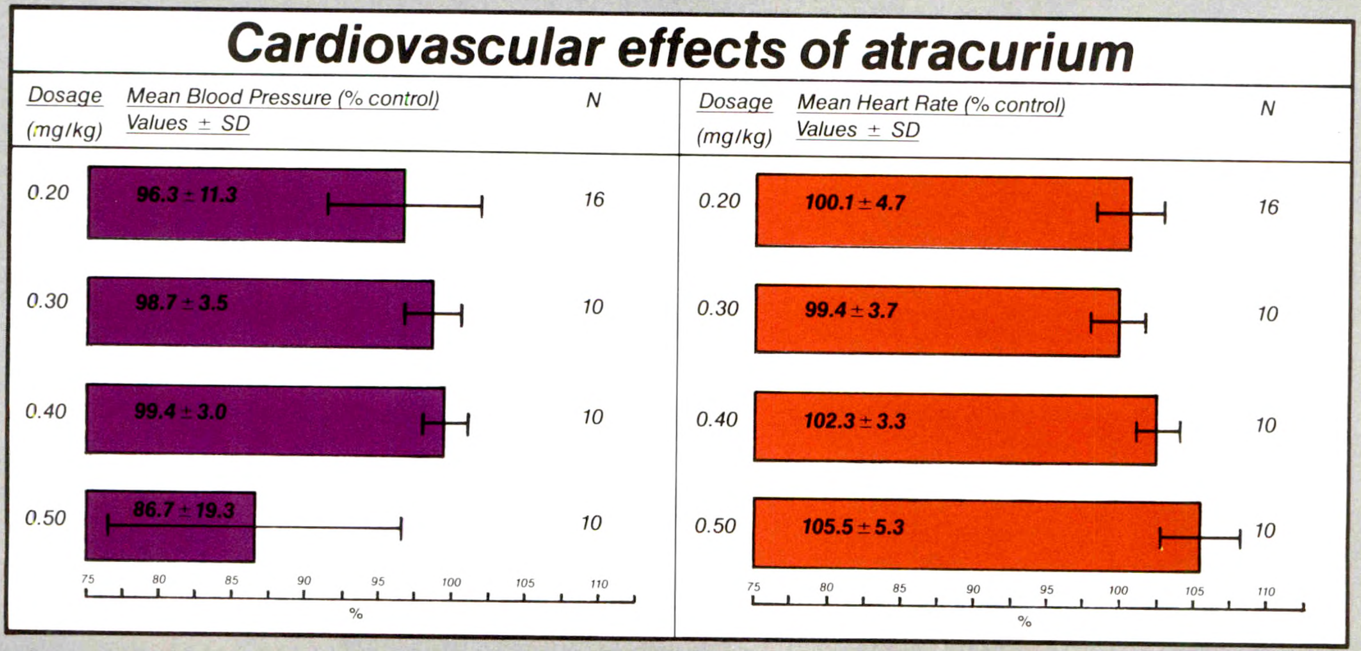
Convenient and Ready to Use

Tracrium is easily administered—requires no premixing.



Few Cardiovascular Effects at Recommended Dosages

☐ Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.



Adapted from Basta et al.[3]

No Cumulative Effects Upon Recovery, After Multiple Doses

☐ Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time

☐ Once recovery begins, it is relatively rapid and independent of dose

☐ This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."[1]

Minimal Histamine Release

☐ Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine

☐ Clinically significant histamine release occurs well within the clinical dosage range (at ED_{95}) for curare, at the upper limits of the clinical dosage range (at 2 × ED_{95}) for metocurine and outside the clinical dosage range (at 3 × ED_{95}) for atracurium[4]

☐ The lack of hemodynamic changes due to Tracrium suggests minimal histamine release

Please see brief summary of prescribing information on the following page.

REFERENCES:

1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. Seminars in Anesthesia 1982; 1:57-62.
2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. Anesth Analg 1982; 61:730-734.
3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 1982; 61:723-729.
4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. Anesthesiology 1982;57:A261.

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TRACRIUM® INJECTION
(atracurium besylate)

TRACRIUM® INJECTION
(atracurium besylate)

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone-marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 2 years have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:
Musculoskeletal: Inadequate block, prolonged block
Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia
Respiratory: Dyspnea, bronchospasm, laryngospasm
Integumentary: Rash, urticaria, reaction at injection site

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

HOW SUPPLIED: Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).

10 ml Multiple Dose Vial (100 mg atracurium besylate per vial). The multiple dose vial contains 0.9% benzyl alcohol added as a preservative. Box of 10 (NDC-0081-0940-95).

Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

U.S. Patent No. 4179507 Printed in U.S.A.

Find out more about
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NITROUS OXIDE/N_2O

Editor: **Edmond I. Eger II, M.D.,** Professor and Vice Chairman for Research, Department of Anesthesia, University of California, San Francisco

After 140 years of use, nitrous oxide is now known to be more than an inert vehicle for other, more potent anesthetics. Nitrous oxide affects the function of every body tissue significantly. Optimum application requires a full appreciation of both the benefits and potential hazards of this anesthetic substance.

Nitrous Oxide/N_2O is a complete resource on the subject. It describes what is known about nitrous oxide – applications and contraindications – and debates its continued clinical use. The current clinical applications of N_2O are reviewed by means of:

- thorough discussion of N_2O pharmacology and distribution
- detailed summary of known side effects and toxicity
- practical guidelines for avoiding and managing these effects

Finally, the case for administering this anesthetic is carefully and candidly assessed in chapters by proponents of both views. ***Nitrous Oxide/N_2O*** is a controversial work that everyone using the drug will want to read.

Contents. Preface. Contributors. A History of Nitrous Oxide. Physics, Chemistry, and Manufacture of Nitrous Oxide. Nitrous Oxide Analgesia. MAC. Nitrous Oxide Delivery Systems. Pharmacokinetics. Respiratory Effects of Nitrous Oxide. Cardiovascular Effects of Nitrous Oxide. Central Nervous System Effects of Nitrous Oxide. Neuromuscular Effects of Nitrous Oxide. Nitrous Oxide in Obstetrics. Metabolism of Nitrous Oxide. Nitrous Oxide Inactivates Methionine Synthetase. Mutagenicity, Carcinogenicity, and Teratogenicity of Nitrous Oxide. Nitrous Oxide Abuse. Toxicity of Nitrous Oxide. The Use of Nitrous Oxide by Dentists. Nitrous Oxide in Veterinary Practice and Animal Research. Controlling Occupational Exposure to Nitrous Oxide. Should We Not Use Nitrous Oxide. We Should Continue to Use Nitrous Oxide. Epilogue. Index.

1984 416 pages 0-444-00860-8 cloth $37.50
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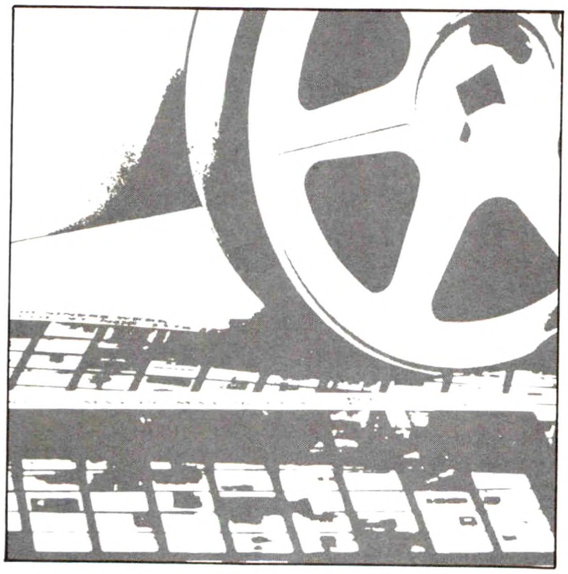

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Anaquest

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Enlon®

(edrophonium chloride injection, USP)

A rapid-acting neuromuscular reversal agent

From the developers of
Ethrane® (enflurane) **and Forane®** (isoflurane)

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60-second reversal
of neuromuscular blockade

- **Onset of reversal significantly faster than with neostigmine or pyridostigmine**—60 seconds versus 7 minutes for neostigmine, 12 minutes for pyridostigmine.[1,2]
- **Duration of reversal comparable to that of neostigmine**—66 minutes versus 76 minutes for neostigmine.[1,2*]
- **Significantly fewer muscarinic side effects and lower atropine requirement than with neostigmine**—edrophonium, 0.5 mg/kg, with only 7 µg/kg atropine, produced minimal change in heart rate or mean arterial pressure compared to noticeable changes in both indexes following neostigmine, 0.04 mg/kg, using *twice* the atropine dose (15 µg/kg).[1,2]
- **May be the preferred reversal agent for atracurium and vecuronium** "...compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and...antagonizes more rapidly residual atracurium-induced neuromuscular blockade."[3]

  "Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug."[4]

***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. Anesthesiology 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 54:375-385, 1982.

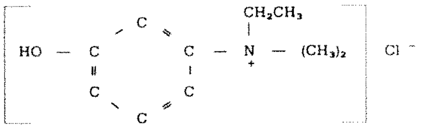
Please see use information on next page.

Anaquest

introduces
Enlon® (edrophonium chloride injection, USP)

DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution:
10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4.

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage. ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers: The safety of ENLON during lactation in humans has not been established.

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anticholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to hypotension;

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia.

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

OVERDOSAGE

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

DOSAGE AND ADMINISTRATION

The recommended adult intravenous injection for antagonism of neuromuscular block:

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:

Adults:

Intravenous Dosage: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dosage: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

Children:

Intravenous dose in children weighing up to 75 pounds:

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

Intravenous dose in children weighing above 75 pounds:

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.
Overtreated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

ENLON (edrophonium chloride injection, USP) Test in Crisis:

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):
NDC 10019-873-15 15 mL multidose vials.

2-85

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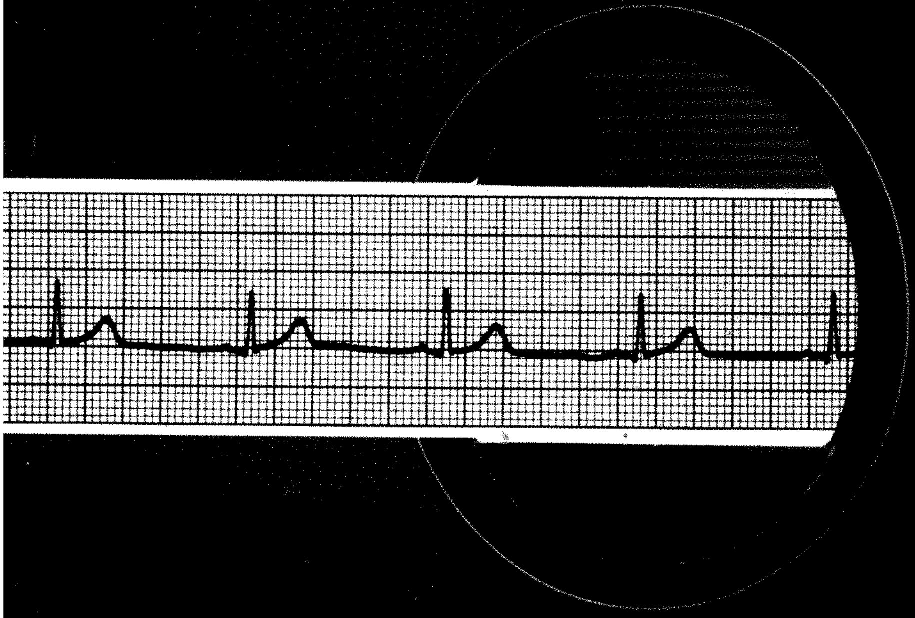

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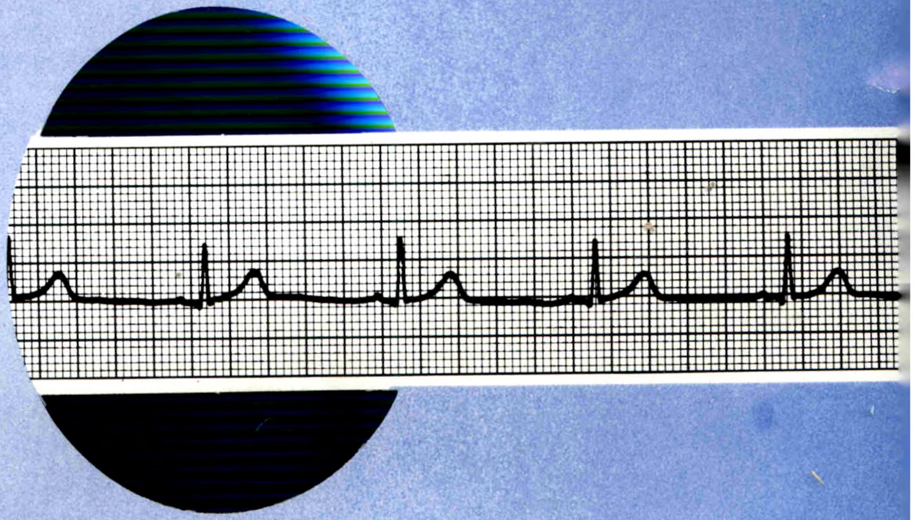

- ○ Substantially improves contractility without adding to myocardial oxygen demand
- ○ Lowers pulmonary capillary wedge pressure and systemic vascular resistance
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*For important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations, please see last page.

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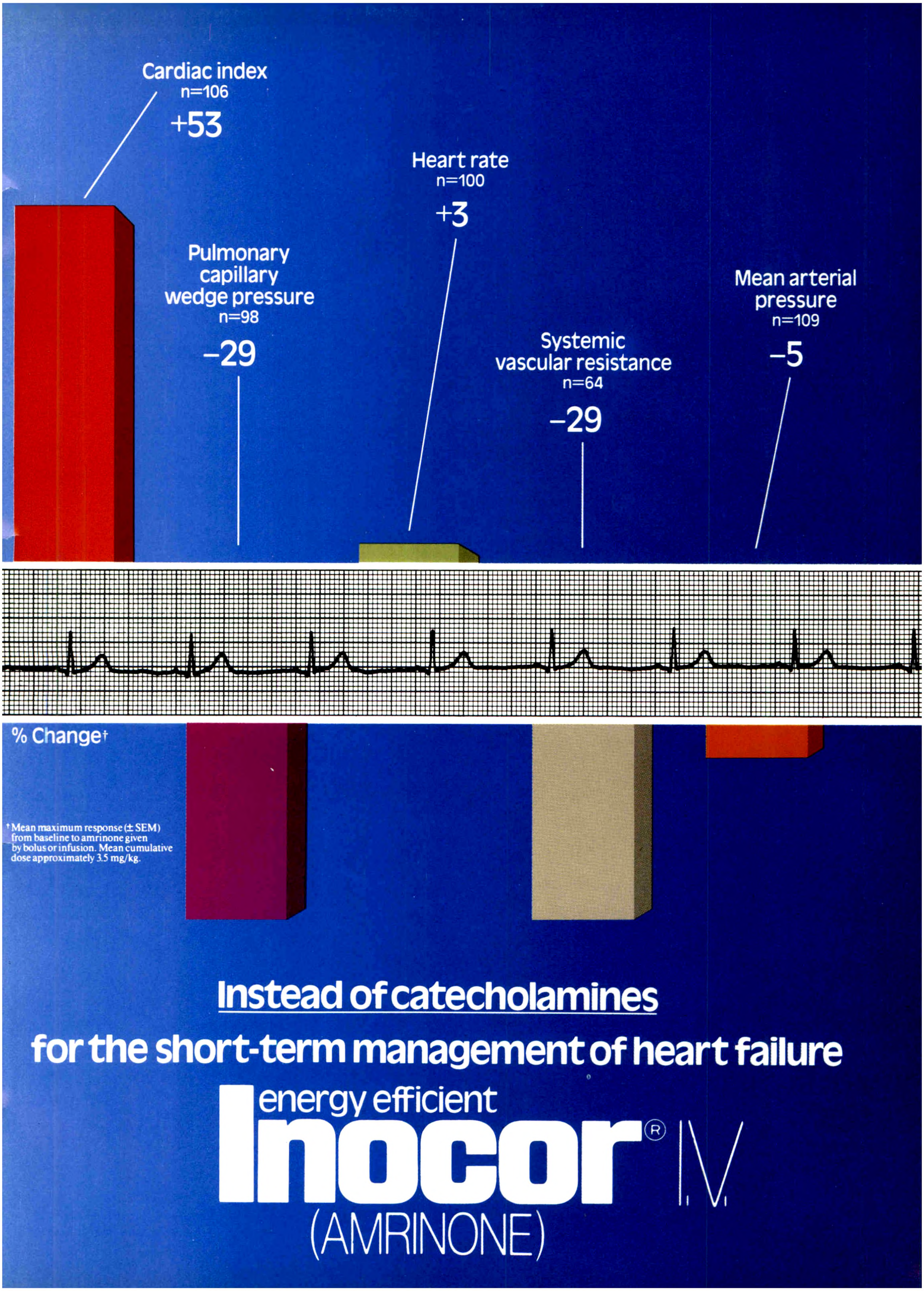

† Mean maximum response (± SEM) from baseline to amrinone given by bolus or infusion. Mean cumulative dose approximately 3.5 mg/kg.

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- Easy to administer

Patients receiving INOCOR should be carefully monitored with the following laboratory studies: platelet counts, liver enzymes, fluid and electrolyte changes, and renal function. Hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General:* INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes* Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol, hydralazine, prazosin, isosorbide dinitrate, nitroglycerine, chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established.

USE IN PREGNANCY *Pregnancy category C* In New Zealand white rabbits, amrinone has been shown to reduce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia* Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm^3 in 2.4% of patients

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%)

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case), myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions* Asymptomatic platelet count reduction (to less than 150,000/mm^3) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications

Should a platelet count less than 150,000/mm^3 occur, the following actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepatotoxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amrinone therapy should be promptly discontinued

If less than marked enzyme alterations occur without clinical symptoms, these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amrinone and reduce the dosage or discontinue the drug based on the usual benefit-to-risk considerations

HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containing INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR lactate equivalent to 5 mg base and 0.25 mg sodium metabisulfite in water for injection

Please see brief summary of product information on this page for contraindications, adverse reactions, patient selection, and precautionary recommendations.

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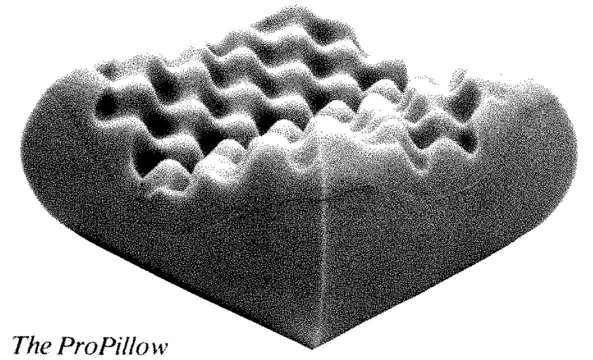

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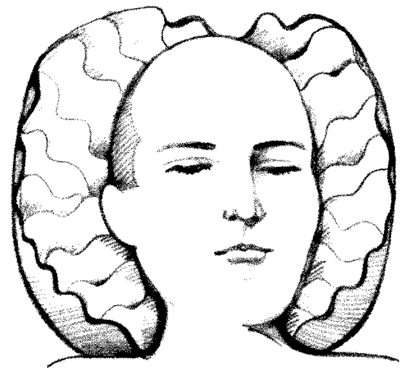

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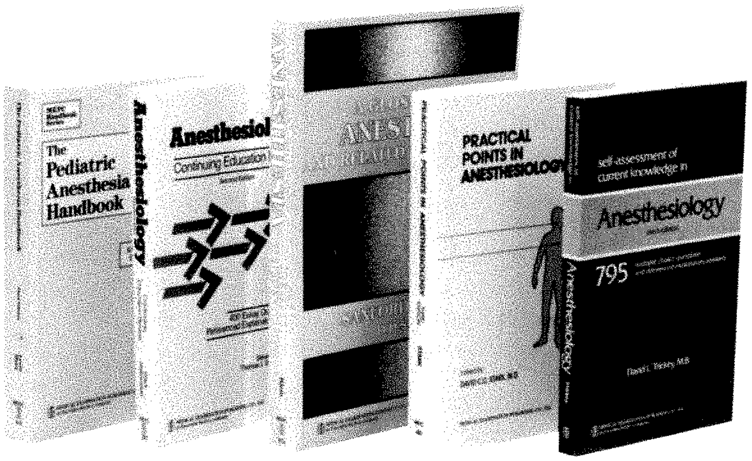
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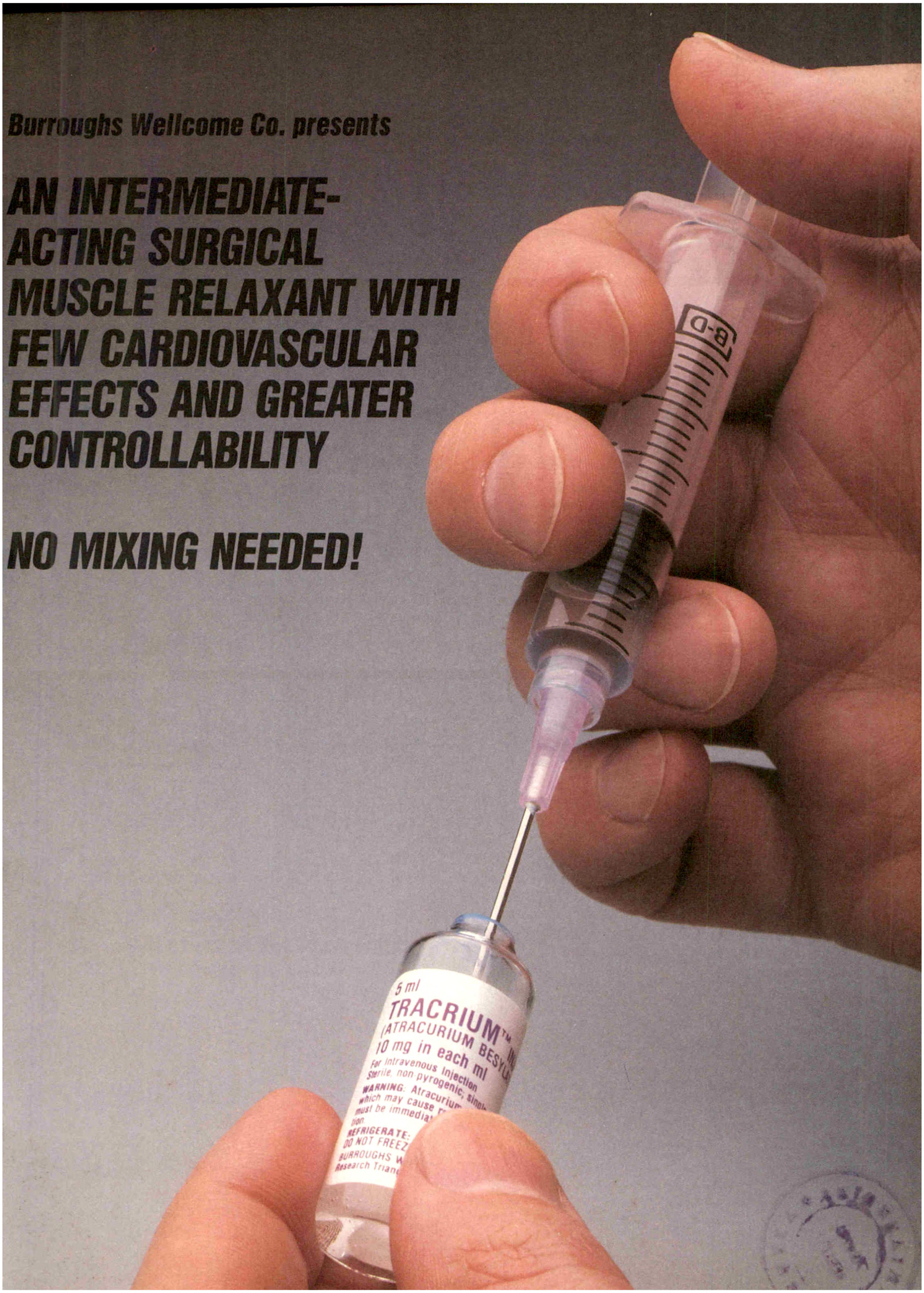

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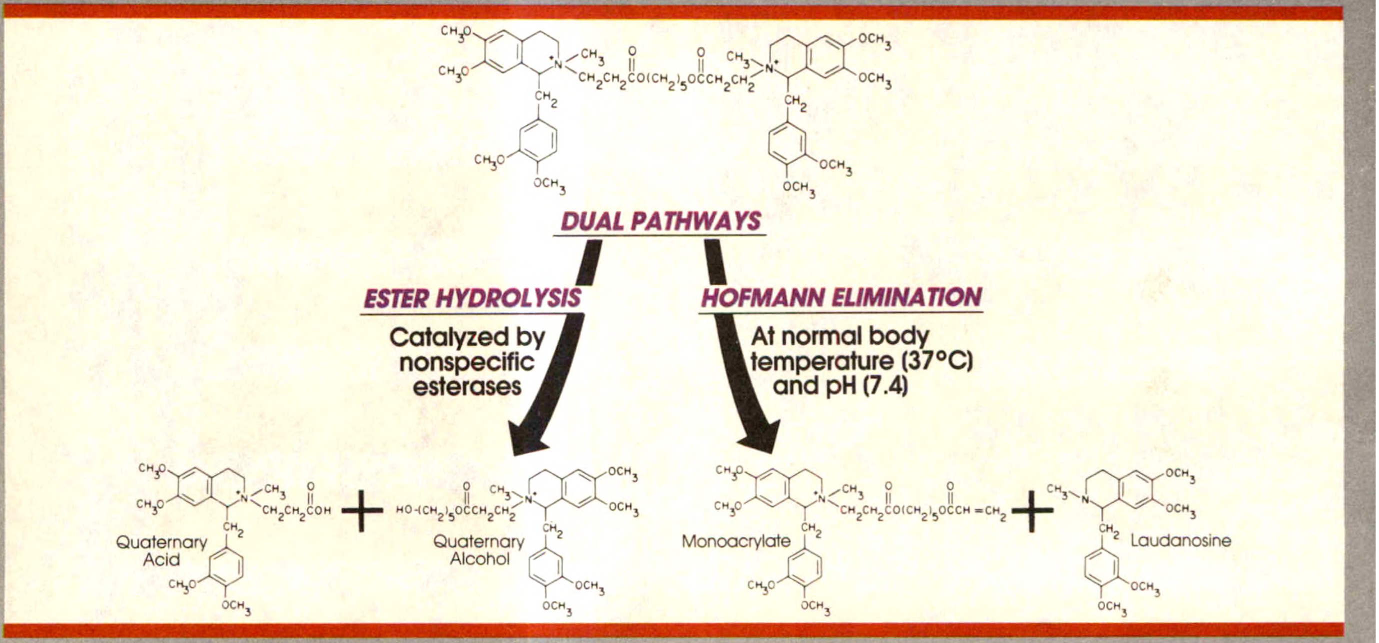


☐ *Tracrium® Injection (atracurium besylate) is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:*

① *Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH*

② *Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required*

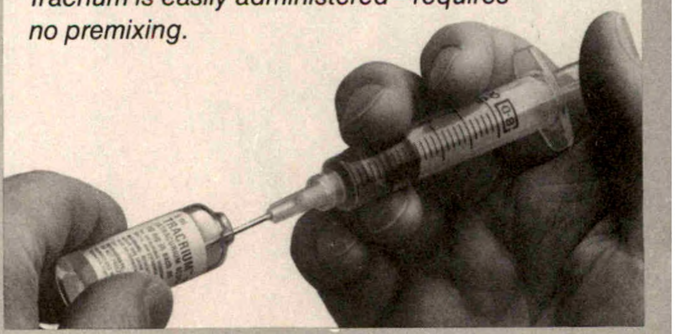
These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."[1]

"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."[2]

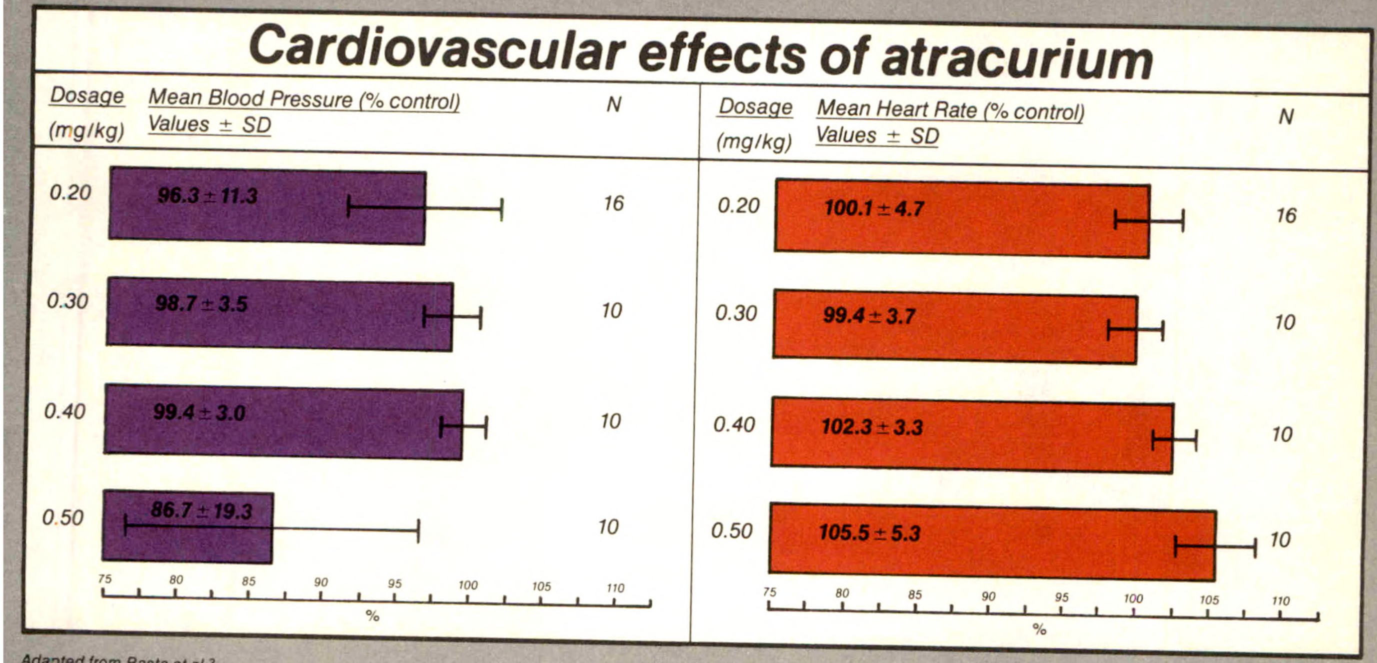
Convenient and Ready to Use

Tracrium is easily administered—requires no premixing.



Few Cardiovascular Effects at Recommended Dosages

☐ Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.



Cardiovascular effects of atracurium

Adapted from Basta et al.[3]

No Cumulative Effects Upon Recovery, After Multiple Doses

☐ Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time

☐ Once recovery begins, it is relatively rapid and independent of dose

☐ This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."[1]

Minimal Histamine Release

☐ Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine

☐ Clinically significant histamine release occurs well within the clinical dosage range (at ED_{95}) for curare, at the upper limits of the clinical dosage range (at 2 × ED_{95}) for metocurine and outside the clinical dosage range (at 3 × ED_{95}) for atracurium[4]

☐ The lack of hemodynamic changes due to Tracrium suggests minimal histamine release

Please see brief summary of prescribing information on the following page.

REFERENCES:

1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. Seminars in Anesthesia 1982; 1:57-62.
2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. Anesth Analg 1982; 61:730-734.
3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 1982; 61:723-729.
4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. Anesthesiology 1982;57:A261.

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TRACRIUM® INJECTION
(atracurium besylate)

TRACRIUM® INJECTION
(atracurium besylate)

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Find out more about
TRACRIUM® INJECTION
(atracurium besylate)
at
The International Anesthesia Research Society Meeting
Las Vegas
March 15-19, 1986

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower, concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 2 years have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:
Musculoskeletal: Inadequate block, prolonged block
Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia
Respiratory: Dyspnea, bronchospasm, laryngospasm
Integumentary: Rash, urticaria, reaction at injection site

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

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Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

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Title: INTRAOPERATIVE LEFT VENTRICULAR WALL MOTION - TRANSESOPHAGEAL 2-D ECHOCARDIOGRAPHIC IMAGE ANALYSIS

Authors: M. D. Abel, M.D., R. A. Nishimura, M.D., M. J. Callahan, M.D., and A. J. Tajik, M.D.
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Introduction. Coronary artery bypass grafting (CABG) affords symptomatic relief of angina and may, in selected subgroups, improve survival (1). However, the effect on both global and segmental left ventricular (LV) function remains unclear. Unchanged, diminished and improved postoperative LV function and wall motion have all been reported following CABG (2). The development of new regional wall motion abnormalities (RWMA) is both a sensitive and early indicator of myocardial ischemia (3). The purpose of this study was to evaluate the different methods available for analysis of RWMA obtained from intraoperative recordings with a two-dimensional (2-D) transesophageal echocardiographic (TEE) probe (4).

Materials and Methods. The procedure was approved by the Institutional Review Board and informed consent was obtained from each patient. Ten males and one female with a mean age of 65 years having CABG were studied. One patient had an aortic valve replacement in addition to CABG for coexistent aortic valve stenosis. The indications for operation were Class III-IV angina in all patients. Six patients had three, four had two, and one patient had single vessel disease, respectively. Eight patients had a previous history of myocardial infarction. Five patients had ejection fractions < 50%. The anesthetic regimen was composed of a narcotic base supplemented with a volatile inhalational anesthetic agent.

A 3.5 mHz transesophageal 9 mm endoscopic probe (Diasonics) was inserted into the patient's esophagus following intubation. The transducer was positioned so as to obtain a LV short-axis view at the papillary muscle level. Adjustments were made on the basis of the relative size of the papillary muscles and the shape of the LV to obtain a true short-axis view. Small adjustments were made throughout the operation to keep the same segment of myocardium in view. Real-time images were displayed on a Diasonics 3400 2-D echocardiographic machine.

Analysis. Recordings were obtained at the following times: before sternotomy, after sternotomy, five minutes after bypass, and skin closure. Representative cycles of the short-axis view of the LV at each of the above four periods were digitized on an echocardiographic computer system (Microsonics). Endocardial and epicardial borders were traced at end-diastole and end-systole. This enabled a fractional area change (FAC)* to be computed. Differences in FAC among the four periods were tested for significance using a paired t-test.

Systolic wall thickening (SWT)† was computed for each quadrant by dividing the myocardium into four segments and using a fixed-external frame of reference.

The digitized cardiac cycles were then transferred to a quad-screen display in order to view all four periods of the operation simultaneously for subjective analysis of wall motion by two independent observers. A five-segment model was used to grade the visual wall motion (5).

Results. Adequate imaging could not be obtained in one patient. There were no complications.

1. Area: The FAC and LV diastolic area changed dramatically during the operative procedure in individual patients. There was no consistent pattern of change overall. The intraobserver variability of FAC was low.
2. Systolic wall thickening: The calculated fractional thickening correlated poorly with the visual analysis of wall motion due to difficulty in identifying the epicardial borders. Further analysis was not done because of large observer variability.
3. Qualitative wall motion analysis: 54% of segments remained unchanged, 26% deteriorated and 20% improved. This outcome was independent of segment location or its preoperative wall motion. Intra- and inter-observer variability analysis showed agreement on wall motion in more than 80% of segments analyzed. There was disagreement on less than 2.5% of segments by two or more grades.

Discussion. The computer-derived LV cavity area and FAC are feasible and reproducible methods for analyzing TEE images obtained during CABG. Serial changes in FAC do not necessarily reflect the intrinsic contractility of the myocardium due to the marked changes in loading conditions occurring throughout the operation. Nonetheless, serial FAC and LV diastolic area provide the anesthesiologist with a relative index of function and volume. Visual qualitative determination of wall motion had a low intra- and inter-observer variability in this study. The ability to detect changes in regional wall motion is enhanced by simultaneously displaying the echocardiographic images obtained at different phases of the operation.

$$*\text{FAC} = \frac{\text{diastolic area} - \text{systolic area}}{\text{diastolic area}}$$

$$\dagger\text{SWT} = \frac{\text{systolic thickness} - \text{diastolic thickness}}{\text{systolic thickness}}$$

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Title: A COMPARISON OF PROPOFOL, THIOPENTAL AND METHOHEXITAL AS INDUCTION AGENTS

Authors: E. C. Abraham, M.D., M. I. Gold, M.D. and C. A. Herrington, R.N.

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Introduction: Propofol (PROP) is a water insoluble intravenous induction agent with a 2.5 minute (min) distribution phase and a 55 min elimination phase[1]. It has been reformulated in an aqueous emulsion offering both efficacy and safety[2]. We wanted to compare PROP with thiopental (TPL) and methohexital (MTX) utilizing cardiovascular, respiratory, and subjective and objective central nervous system variables.

Methods: After institutional approval and informed consent, 113 male, ASA 1 and 2 patients had either 2.5 mg/kg PROP (n = 39), 4.0 mg/kg TPL (n = 38),or 1.5 mg/kg MTX (n = 36) in a random, open-label fashion. After premedication I.M. with diazepam, meperidine, and glycopyrrolate, an infusion of D_5W was started in a large vein. Monitors included: lead II EKG from which pulse (HR) was measured, an Accutor #1, with cuff placed on the arm opposite the I.V. and systolic and diastolic blood pressure (SBP and DBP) printout. End-tidal CO2 (ET CO2) was measured with a SARA Mass Spectrometer. A stopwatch was used. The agent was administered during 20 seconds and each patient counted; when verbal contact, confirmed by eyelash reflex disappeared, induction was considered finished (efficacy excellent). If the patient did not fall asleep, or awakened, half the induction dose was repeated (efficacy good). Assessment of physiologic variables was made for three min post-injection. At the end of three min succinylcholine 1.5 mg/kg was administered, the patient intubated and N_2O - O_2 (3L/2L) with isoflurane given. The following were recorded: HR,SBP, DBP, respiratory rate (RR), ET CO2, times for induction, onset of apnea, incidence of apnea, awakening, response and orientation. Discomfort on injection, signs of CNS excitation, hiccoughs, significant EKG or laboratory changes and ability to induce anesthesia without reinjection were noted. The data were analyzed with standard chi-square tests, Cox regression models, log-rank tests and logistic regression. With the number of patients used, any differences in response of 20% could be detected with the power of 0.25 and a type 1 error of 0.05.

Results: See Tables 1, 2, and 3. No different times for induction occurred between groups. However, TPL was associated with a longer awakening and response time than MTX while PROP had a faster orientation time than TPL. PROP was associated with a slower pulse than MTX as was TPL. On the other hand, PROP had lower SBP's and DBP's than did TPL and MTX. PROP also was associated with a slower RR than were the other two. Although more CNS excitatory activity occurred with PROP this was not statistically significant. There were seven incidences of hiccoughs with MTX and none for the other two agents. Only four patients receiving PROP required additional induction dose (half) while almost a dozen of each of the other two groups did ($p < 0.05$).

Discussion: Although PROP has held potential as an induction agent because of its rapid action, short duration and fast recovery, its introduction has been slow. This comparison of PROP, TPL and MTX demonstrated some differences in CNS effects such as PROP's faster orientation time when compared with TPL and PROP's significantly better efficacy i.e., less additional induction agent. Four mg/kg of TPL and 1.5 mg/kg MTX may be insufficient. There were more signs of CNS excitation with PROP and MTX when compared with TPL (not statistically significant). PROP had a more stable HR but a lower DBP and SBP than the two barbiturates. The high incidence of hiccoughs with MTX makes it disadvantageous. In conclusion, all of these induction agents have advantages and disadvantages; PROP proved to be a safe and effective anesthetic which is an alternative to TPL and MTX.

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Table 1: Onset and Recovery from Anesthesia

	Time (sec)	Time (min)		
Drug	Induction	Awakening*	Response**	Orientation***
PROP	34 ± 1	19 ± 2	21 ± 2	31 ± 3
TPL	35 ± 1	24 ± 3	26 ± 3	41 ± 4
MTX	32 ± 2	17 ± 2	19 ± 2	33 ± 4

*TPL vs MTX $p < 0.03$ **TPL vs MTX $p < 0.05$
***PROP vs TPL $p < 0.05$

Table 2: Cardiovascular and Respiratory Effects

Drug	* ^HR (/min)	** ^SBP (mm Hg)	** ^DBP (mm Hg)	*** ^RR (/min)	P ET CO2^ (mm Hg)	Apneic Patients
PROP	+5.4 ± 2	-11.9 ± 2	-6.9 ± 1	-7.4 ± 1	-1.0 ± 1	37
TPL	+8.6 ± 2	- 1.7 ± 2	+3.6 ± 1	-5.0 ± 1	-2.7 ± 1	31
MTX	+19.3 ±2	- 0.7 ± 2	+2.3 ± 1	-5.0 ± 1	-1.0 ± 1	31

^Mean Change, ± Standard Error of the Mean
*PROP and TPL vs MTX $p < 0.01$
**PROP vs TPL and MTX $p < 0.01$
***PROP vs TPL and MTX $p < 0.02$

Table 3: Adverse Effects and Efficacy (Repeat Induction Dose)

DRUG	Discomfort Injection	Excitatory Activity	* Hiccoughs	Efficacy**	
				Excellent	Good
PROP	3	12	0	35	4
TPL	3	4	0	27	11
MTX	2	9	7	24	12

*MTX vs TPL and PROP $p < 0.01$
**See Text for criteria.PROP vs TPL and MTX $p < 0.05$

Title: KETAMINE: AN ALTERNATIVE FOR THE ANESTHETIC MANAGEMENT OF ACUTE EPIGLOTTITIS

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Introduction. Epiglottitis is an infectious disease which can rapidly progress to acute airway obstruction. There are two common methods for the anesthetic management of epiglottitis. Awake intubation with a rigid bronchoscope or endotracheal tube with subsequent delivery of anesthetic gases is one recommended method. An alternative technique is an oxygen/halothane mask induction followed by endotracheal intubation. Review of our management of epiglottitis over a twelve year period has convinced us that the use of ketamine represents a safe alternative method of handling this problem.

Methods. We reviewed the charts of children with a discharge diagnosis of epiglottitis from the years 1973 through 1984. Our Committee on Human Investigation approved the review.

When epiglottitis was suspected, the staff anesthetist was consulted and the history and physical were evaluated. When appropriate, intubation was carried out for airway support. Intubations were performed by staff anesthetists (92%), anesthesia fellows (3%), anesthesia residents (4%), or pediatric residents (1%).

Following intubation, a leak around the endotracheal tube was checked and position confirmed by chest x-ray. The patient was transferred to the pediatric intensive care unit and kept sedated. When the patient was afebrile the epiglottis was examined at the bedside to demonstrate that edema had subsided and extubation was indicated.

We tabulated the success of intubation, the complications of intubation, anesthetic technique and eventual hospital course for the following three groups shown in Table 1: Ketamine anesthesia; other anesthetics ("ANES"); and awake intubation. Analysis of variance followed by the appropriate critical value test for multiple comparisons was used to compare the 3 groups. P values less than 0.05 were considered the minimal level for statistical significance.

Results: Intubation was performed in 107 of 111 patients. One patient required intubation twice because of premature self-extubation. Three patients were observed without an endotracheal tube. One child needed an emergency tracheostomy after a failed attempt at awake intubation at another institution. No patient required tracheostomy because of failed intubation in our institution. There were no deaths attributable to upper airway obstruction. Six patients intubated at outside institutions were not included in our analysis.

TABLE 1

	Ketamine	Anes.*	Awake
Total number pts. intubated	58 57%	19 19%	24 24%
Mean Age (S.D.)	3.1 (2.3)	2.9 (2.0)	2.9 (1.5)
Intubated 1st Attempt	55 95%	16 84%	21 88%
Vomiting on induction	0 0%	1 5%	1 4%
Racemic Epinephrine following extubation	5 9%	2 11%	6 25%
Mean duration of intubation (days) (S.D.)	3.2 (1.4)	3.5 (1.0)	3.7 (1.7)

*Alternate anesthetic approaches included neuromuscular blockade, halothane, and sedatives.

The ketamine group did not differ in any significant manner from children intubated with other techniques. The mean ketamine dose was 2.5 mg/kg with a range of 0.8 - 5.4 mg/kg. Secretions were minimized pre-intubation using atropine in 84% of the ketamine group.

Conclusion.
Anesthetic management of the pediatric airway emergency of epiglottitis should emphasize safety and rapidity of establishing the airway.

1) In our experience ketamine represents an acceptable alternative technique for the anesthetic management of epiglottitis.
2.) All cases in which ketamine was used were successfully and safely intubated in the Emergency Room. This represents an average saving of $250 operating room time. This eliminates the potential danger involved in transporting patients to the Operating Room.

There is no one method of treating epiglottitis. Ketamine has been disparaged as an agent for airway management because of the possibility of increasing airway reflexes and provoking vomiting. In our experience, neither theory has proven valid. Ketamine provides safe rapid access to the endangered airway.

Title: **CHANGES OF FRESH GAS FLOW AFFECT THE TIDAL VOLUME DELIVERED BY ANESTHESIA VENTILATORS**

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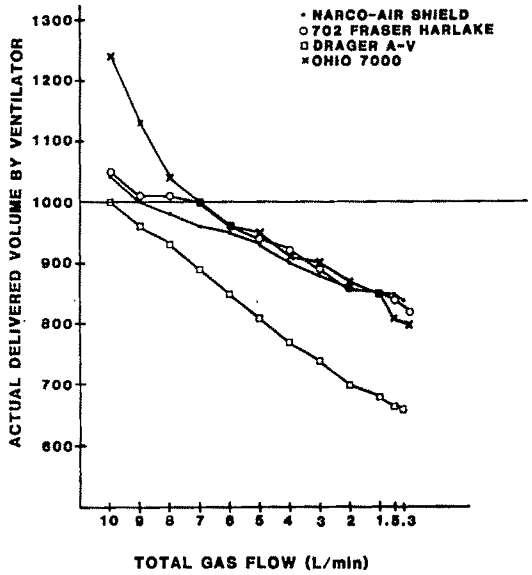
Introduction. There is a general consensus that with most ventilators used during anesthesia, changes of fresh gas flows (FGF) fed from the anesthesia machine into the breathing circuit, do not alter the tidal volume (V_t) delivered to the patient, as long as the ventilator settings are unaltered (1,2). However, observations made by Ghani (3), at 2.5 and 10 L/min of FGF, suggested a significant difference in V_t at these two levels. In a step-down fashion, we measured the performance of four different ventilators (Narco Air Shields, 702 Fraser Harlake, Dräger A-V, and Ohio 7000) from 10 to 0.3 L/min having found marked unpredictability in their performance when FGF were changed.

Methods. A Fraser Harlake respirometer was attached proximally to the Y-piece of the breathing circuit and distally to a breathing bag with a corrugated tube of approximately 100 cm to simulate the clinical condition. Starting from 10 L/min, FGF were decreased one liter at a time down to 1.0 L/min making measurements at each level and also at 0.5 and 0.3 L/min, using a constant I:E ratio 1:2. At each level, the displacement of the bellows was confirmed as being 1000 ml/breath and the frequency 10/min, measurements of peak pressure, delivered V_t and minute volume (V) were made using four different ventilators.

Results. All ventilators failed to consistently deliver V_t as indicated by bellows displacement when FGF were varied. All ventilators except the Dräger A-V delivered more than 1000 ml at FGF of 10 L/min; the Ohio 7000 delivered a V_t 24% higher. The optimal point (at which the actual V_t equaled precisely bellows displacement) varied with each ventilator. With stepdown decreases of FGF, there was a progressive reduction of delivered V_t; the worst performance was seen with the Dräger A-V which delivered only 660 ml at 0.3 L/min (Figure). These results showed:
$r = .998$ and $p<.001$ (for V_t /FGF) and $r = .994$ and $p< .001$ (for peak pressure /FGF).

Discussion. The effective V_t of the ventilators studied was observed to be significantly different from that shown on the bellows displacement settings when FGF were varied. At 10 L/min FGF, of the four ventilators studied, three delivered larger V_t than indicated; below 7 L/min of FGF, all of them delivered less than indicated. The incorporation of an expiratory spirometer is recommended to precisely verify the V_t received by anesthetized patients having their respiration controlled mechanically.



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Title: FURTHER EVIDENCE FOR CENTRAL 5-HT PARTICIPATION IN SUFENTANIL-REDUCED MAC

Authors: J. S. Althaus, M.S., E. D. Miller, Jr., M.D., C. A. DiFazio, M.D., Ph.D., J. C. Moscicki, M.S., and J. S. Engle, B.S.

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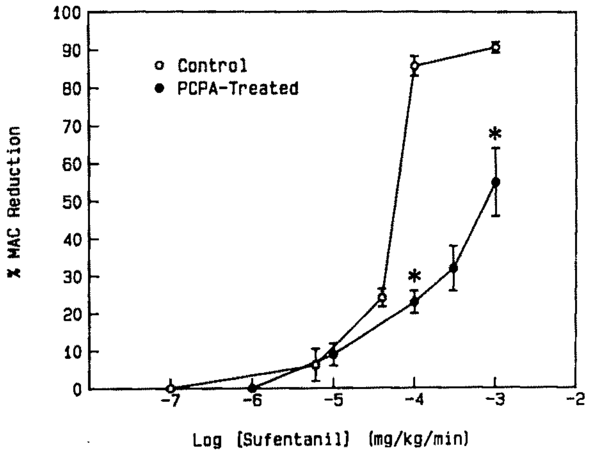
Introduction. We have shown in rats that sufentanil produced a dose-dependent reduction in halothane MAC with a maximum reduction of greater than 90%. In addition, serotonin (5-HT), but not catecholamines (CA), were depleted in the cord and medulla of these rats after receiving high doses ($\geq 1 \times 10^{-4}$mg·kg^{-1}·min^{-1}) of sufentanil compared to low doses ($\leq 7\ 10^{-5}$mg·kg^{-1}·min^{-1}) of sufentanil. This evidence supports the hypothesis that sufentanil may contribute to an analgetic component of general anesthesia by modulating nociception via the release of 5-HT. To test this hypothesis further and to identify the nature of the analgetic component, a dose response curve of halothane MAC reduction vs sufentanil doses was determined using rats depleted of central 5-HT with parachlorophenylalanine (PCPA). If the function of central 5-HT is an important component of halothane MAC reduction with sufentanil, then depletion of central 5-HT may identify that component and possibly reduce the anesthetic potency of sufentanil.

Methods. Eight Sprague-Dawley rats weighing between 275-325 gms were each given a single injection of 200 mg·kg^{-1} of PCPA IP 48 hours prior to each experiment. Rats were then anesthetized with halothane, intubated, and ventilation controlled with a Harvard animal respirator. Arterial blood gases were maintained normal throughout each experiment. The femoral artery and vein were cannulated using PE50 tubing. Heart rate and colonic temperature were monitored. Concentrations of halothane, sampled from the lungs, were assayed by gas chromatography. Halothane MAC in the presence and absence of sufentanil was established. MAC was considered to be the point midway between the highest concentration of halothane that produced a positive test and the lowest concentration of halothane that produced a negative test to tail clamp. After an intravenous bolus that was three times the subsequent infusion rate, sufentanil was administered in doses ranging from 10^{-6}mg·kg^{-1}·min^{-1} to 10^{-3}mg·kg^{-1}·min^{-1} by continuous infusion. At the conclusion of each experiment, brains were removed and the hypothalamus, medulla, and cord (C1 to C5) were dissected and assayed for CA and 5-HT by HPLC with electrochemical detection. Standard statistical tests were used to analyze data.

Results. Central 5-HT was depleted by greater than 70% with PCPA while central CA were minimally affected by this treatment. The pre-sufentanil MAC of 0.70 vol% ± .03 for PCPA-treated rats was not different ($p<.05$) from the pre-sufentanil MAC for control rats previously reported. In the figure, the dose-response curve for PCPA-treated rats generated in this study is superimposed onto the dose-response curve for control rats determined previously. At low doses of sufentanil ($\leq 10^{-5}$mg·kg^{-1}·min^{-1}), % MAC reduction was not affected by the PCPA treatment. Conversely, at high doses of sufentanil ($\geq 10^{-4}$mg·kg^{-1}·min^{-1}), % MAC reduction was significantly ($p<.05$) diminished by the PCPA treatment. The ED_{50} value (extrapolated from the linear portion of the dose-response curve) of 8.5×10^{-4}mg·kg^{-1}·min^{-1} for PCPA-treated rats was more than tenfold greater than the ED_{50} value for control rats.

Discussion. This study clearly showed that 5-HT function was an important factor in the reduction of halothane MAC by sufentanil. Depletion of central 5-HT with PCPA caused a decrease in the anesthetic potency of sufentanil as indicated by an increase in the ED_{50} for MAC reduction from 6.5×10^{-5}mg·kg^{-1}·min^{-1} to 8.5×10^{-4}mg·kg^{-1}·min^{-1}. The authors recognize that there may exist more than one possible mechanism for the analgetic effects of narcotics. In this case, reductions in central 5-HT, although quite extensive, were not reflective of equivalent reductions in the potency of sufentanil. In addition, the decrease in potency of sufentanil was not characterized by a simple shift in the dose-response curve of the control. Depletion of central 5-HT was most effective at mid-range doses and less effective at very low and very high doses of sufentanil. At these extremes of the dose-response curve, MAC reduction may proceed by mechanisms not involving 5-HT function. Nevertheless, the data show that the anesthetic potency of sufentanil was diminished by PCPA-depleted stores of releasable 5-HT. Furthermore, the nature of the analgetic component may involve 5-HT function at mid-range doses of sufentanil. We conclude that sufentanil contributes to an analgetic component of general anesthesia by modulating nociception via the release of 5-HT.



*p<0.05 compared to control

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Title: PARTIAL PRESERVATION OF CEREBRAL VASCULAR RESPONSIVENESS TO HYPOCAPNIA DURING ISOFLURANE-INDUCED HYPOTENSION IN DOGS

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Introduction. 1.5 - 2.5 MAC end-expired isoflurane (ISF) has been proposed as a desirable treatment to produce elective hypotension because of the cerebral protective effect of ISF during conditions of reduced oxygen and substrate delivery (1). However, when elective hypotension is used for neurological surgery, or for cases where ICP is of concern, hypocapnia frequently is used along with the hypotensive treatment. Currently available data suggest that there may be some hazard in combining hypocapnia with 1.5 - 2.5 MAC ISF for elective hypotension. Previous studies at 1 MAC ISF reported that ISF enhances the cerebral vasoconstriction caused by hypocapnia, reducing cerebral blood flow (CBF) to near "critical" levels (2). If hypocapnia also causes cerebral vasoconstriction during ISF-induced hypotension, CBF may be reduced to below "critical" levels resulting in cerebral ischemia. The present study was designed to examine whether CBF decreases with hypocapnia during ISF-induced hypotension in dogs, and if so whether CBF is reduced to below "critical" levels.

Methods. Twelve dogs were anesthetized with isoflurane (1.5 MAC) and ventilated to maintain Pa_{O_2} > 120 mm Hg and Pa_{CO_2} = 40 mm Hg. A femoral artery was cannulated for blood sampling for blood gas analyses and continuous monitoring of mean arterial pressure (MAP) and heart rate. The posterior saggital sinus was cannulated for direct measurement of CBF. Expired CO_2 was continuously monitored using a Beckman LB-2 medical gas analyzer. At completion of the surgical procedure, the concentration of isoflurane was decreased to 0.2 MAC. After stable baseline measurements were observed, six of the twelve dogs (Group I) were examined at normotension with and without hypocapnia (hypocapnia = Pa_{CO_2} 20 mm Hg). Next the concentration of ISF was increased until MAP was reduced to 50 mm Hg. Systemic and cerebral values were determined at hypotension with and without hypocapnia. Each condition was maintained for 30 min before cerebral and systemic values were determined. The remaining six dogs (Group II) were examined at ISF-induced hypotension to MAP of 50 mm Hg without prior testing of CO_2 responsiveness at normal MAP. This group was included to rule out the possibility that in the first group the CBF response to normocapnia and hypocapnia during hypotension was influenced either by time (2 hr elapsed before hypotension was induced) or by the 30 min exposure to hypocapnia at normal MAP. After testing at ISF-induced hypotension, systemic and cerbral values were determined at sodium nitroprusside (SNP)-induced hypotension to MAP of 50 mm Hg. Cerebral vascular resistance (CVR) was calculated as the ratio of MAP and CBF. Statistical comparisons were made using analysis of variance for repeated measures with $p < 0.05$ considered significant.

Results. During normotension, hypocapnia significantly increased CVR (by 82%), and decreased CBF (by 43%) in Group 1 (Table). In the same dogs, during ISF-induced hypotension, hypocapnia still caused a significant increase of CVR (by 28%), though the increase was less than that caused by hypocapnia at normal MAP. Also, during ISF-induced hypotension, hypocapnia still caused a significant decrease of CBF (by 22%), though the decrease was less than that caused by hypocapnia at normal MAP. In Group II the cerebrovascular responses to hypocapnia during ISF-induced hypotension were similar to those observed in Group I. In contrast, no statistically significant change in CVR or CBF occurred with hypocapnia during SNP-induced hypotension. End-expired ISF values for Groups I and II at MAP of 50 mm Hg were ~ 1.7 MAC. The magnitudes of the arterial blood pH increase and bicarbonate decrease were not significantly different between groups.

Discussion. The results suggest that the cerebrovasodilation accompanying ISF-induced hypotension attenuates but does not completely override the cerebrovasoconstrictor response to hypocapnia. In contrast, in previous studies from this laboratory the cerebrovasoconstrictor response to hypocapnia was completely abolished at MAP of 50 mm Hg induced with SNP, trimethaphan, or nitroglycerin. In theory, the reduction of CBF caused by hypocapnia during ISF-induced hypotension may increase the risk for ischemia. However, CBF values during hypotension plus hypocapnia (39.4 ± 4.8 $ml \cdot min^{-1} \cdot 100\ g^{-1}$, mean ± SD) were well above "critical" levels. The present results imply that hypocapnia may be used to decrease cerebral blood volume to improve operative conditions during ISF-induced hypotension for neurological surgery.

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Table. Cerebral and Systemic Values, Group I (mean ± SD)

	Norm MAP Pa_{CO_2}=40	Norm MAP Pa_{CO_2}=20	MAP=50 Pa_{CO_2}=40	MAP=50 Pa_{CO_2}=20
CVR, $mmHg/ml \cdot min^{-1} \cdot 100\ g^{-1}$	1.30±0.34	2.36±0.71[a]	0.98±0.13[a]	1.25±0.13[b]
CBF, $ml \cdot min^{-1} \cdot 100\ g^{-1}$	81.4±21.3	46.2±13.7[a]	50.0±6.5[a]	39.4±4.8[b]
$PsSO_2$,[c] mmHg	58±11	34±7[a]	50±7	35±5[b]
MAP, mmHg	106±12	108±13	48±1[a]	49±2
Pa_{CO_2}, mm Hg	41.0±2.7	22.4±1.7[a]	41.9±2.6	23.9±1.9[b]
pH	7.34±0.04	7.49±0.04[a]	7.26±0.03	7.43±0.04[b]
Bicarbonate, mEq/ℓ	21.7±1.8	17.0±2.1[a]	18.6±1.9	15.8±1.7[b]

a=significant difference vs. normMAP and Pa_{CO_2}=40, $p<0.05$
b=significant difference vs. MAP=50 and Pa_{CO_2}=40, $p<0.05$
c=saggital sinus blood oxygen tension

Title: BUNEGIN-ALBIN CVP CATHETER IMPROVES RESUSCITATION FROM LETHAL VENOUS AIR EMBOLISM IN DOGS

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Introduction. Controversy exists between those who advocate placement of pulmonary artery (PA) catheters and those who prefer right atrial (RA) catheters for treatment of venous air emboli (VAE). One issue in this controversy that has not been addressed is whether the small single lumen of the CVP port of PA catheters would present a clinically significant impairment in the ability to aspirate VAE. Regarding RA catheters, there is also uncertainty as to the clinical efficacy of single-orifice versus multi-orifice catheters. Using an in vitro casting of a human atrium, Bunegin et al. examined the retrieval of "intravascular" air with single- and multi-orifice long-line catheters (1). Significantly greater proportions of VAE were retrieved with multi-orifice catheters than with single-orifice catheters. The authors speculated that these results may have implications for choice of catheter and location of catheter tip in clinical practice, but concluded that in vivo studies were needed. The present study was designed to determine a supralethal dose of VAE for dogs and to examine retrieval of a fatal VAE dose with commonly used single- and multi-orifice long-line catheters in dogs. Catheters were evaluated for 1) proportion of VAE retrieved, and 2) success rate of resuscitation from VAE.

Methods. 38 dogs were anesthetized with isoflurane (> 1.7%) and N_2O (66%) in O_2, and ventilated to maintain $Pa_{O_2} > 120$ mm Hg and $Pa_{CO_2} = 40$ mm Hg. Expired CO_2 was continuously monitored using a Beckman LB-2 medical gas analyzer. A femoral vein was cannulated for fluid administration and for infusion of air. At the completion of the surgical procedures, dogs were placed in the prone position with the head elevated, and the concentration of isoflurane was decreased to 0.3% (N_2O unchanged). After stable baseline measurements were observed, dogs were assigned to one of six groups for intravenous infusion of air.

Determination of lethal dose. In Groups I and II no long-line catheter was placed. Group I was given 3 ml/kg air over 20 sec (n=5), and Group II was given 5 ml/kg air over 30 sec (n=6). **Evaluation of catheters.** First VAE. In the remaining four groups long-line catheters were placed and dogs were given 5 ml/kg air over 30 sec. For Group III (n=7) a single-orifice catheter was placed but was not used to retrieve air. This group served as the control group for Groups IV-VI. In Groups IV-VI attempts to aspirate VAE were begun at the first recognizable fall in expired CO_2 following intravenous injection of air. The catheter used for Group IV (n=7) was a single-orifice Sorensen® CVP kit catheter (catheter lumen cross sectional area ~ 1.4 mm^2). The catheter used for Group V (n=9) was the CVP port of an Edwards® 7 Fr PA catheter (lumen area ~ 0.2 mm^2). The catheter used for Group VI (n=7) was a multi-orifice Bunegin-Albin air aspiration CVP set (Cook®) (lumen area ~ 1.8 mm^2). Single-orifice catheters were positioned with the tip just above the junction of the SVC and RA, and multi-orifice catheters were positioned with the tip just below the junction of the SVC and RA (1). The catheter tip was located in the desired position according to the EKG trace obtained by filling the catheter with a bicarbonate solution and using the catheter tip as an exploring EKG electrode. Second VAE. 10 min after the first VAE, a second administration of 5 ml/kg air was given to all dogs successfully resuscitated from the first VAE. As before, aspiration of catheters to retrieve air was begun at the first recognizable fall in expired CO_2. Proportions of air retrieved were compared between Groups IV - VI using Student's t-test for unpaired samples. Incidences of successful resuscitation were compared between Groups III-VI using the variance ratio test. A P value < 0.05 was considered significant.

Results. When a venous catheter was not used for treatment of VAE, 4 of 5 dogs survived infusion of 3 ml/kg air, whereas 0 of 13 untreated dogs survived infusion of 5 ml/kg of air. First VAE. In the treated dogs, a significantly greater proportion of the 5 ml/kg VAE was retrieved with the multi-orifice catheter than with either of the two single-orifice catheters (Table). The incidence of successful resuscitation from VAE also was significantly higher with the multi-orifice catheter (6 of 9 dogs) than with either single-orifice catheter (0 of 7 with the Sorensen catheter, 1 of 7 with the CVP port of the PA catheter). Second VAE. Dogs that were successfully resuscitated from one episode of VAE also could be resuscitated from a second episode of VAE when the multi-orifice catheter was used (4 of 6 dogs resuscitated, 54 ± 12% of air retrieved) but not when a single-orifice catheter was used (0 of 1 dog resuscitated, 2% of air retrieved).

Discussion. Under the conditions of this study 3 ml/kg was sublethal for most dogs while 5 ml/kg was always lethal for untreated dogs. Only treatment of VAE by aspiration through the multi-orifice catheter allowed retrieval of most of the intravenously infused air and successful resuscitation of most dogs. Single-orifice catheters were largely ineffective for either purpose. These results support the speculation of Bunegin et al. that the choice of venous catheter and position of the catheter may have clinical implications for aspiration of VAE (1). However, because retrieval of VAE varies according to catheter tip location and patient position (1), it is possible that single-orifice catheters might perform as well as multi-orifice catheters under conditions different from those used here.

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Table. Responses to first 5 ml/kg VAE

Catheter	N	Proportion of air retrieved (mean ± SEM)	Incidence of successful resuscitation
None present	6	—	0%
Present but not used	7	—	0%
Sorensen® CVP kit catheter	7	16±6%	0%
CVP port of PA catheter	7	4±1%	14%
Cook® antecubital CVP catheter	9	60±7%*	67%#

* Significant difference compared to aspiration of air via single-orifice catheters, $p < 0.05$.

# Significant difference compared to other groups of dogs given 5 ml/kg air, $p < 0.05$.

Title: THIOPENTAL AND EPINEPHRINE-INDUCED VENTRICULAR ARRHYTHMIAS WITH ENFLURANE OR ISOFLURANE IN DOGS

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Introduction. Thiopental induction reduces the arrhythmic dose of epinephrine (ADE) with cyclopropane and halothane, which effect persists for up to four hours (1,2). While ADE's and corresponding plasma epinephrine levels (PLE) have been compared with halothane and enflurane (3), they have not with isoflurane. Nor has the effect of thiopental on ADE's and PLE's with enflurane and isoflurane been reported.

Methods. Healthy mongrel dogs (N=8) were tested on each of four occasions at least three days apart: 1. ENF = enflurane 2.75% end-tidal (ET), 2. ENF-THIO = enflurane (2.75% ET) following thiopental (THIO) induction (20 mg/kg), 3. ISO = isoflurane 1.88% ET, 4. ISO-THIO = isoflurane (1.88% ET) following THIO induction. These anesthetic levels, equivalent to 1.25 MAC for the dog, were maintained for at least 30 min prior to testing. Dogs were mechanically ventilated with oxygen and anesthetic, and CO_2 ET kept between 35 and 40 torr. Sodium bicarbonate was administered to correct base deficits $\geq$ 3 meq/l. Esophageal temperature ranged from 36.0 to 38.5°C. Epinephrine (EPI) infusions between one and 10 µg/kg/min lasted for three minutes if there were no ventricular arrhythmias. The ADE (µg/kg) for ventricular arrhythmias (four or more extrasystoles within 15 sec) was determined as the product of infusion rate and time (min) to arrhythmia. Arterial sampling for plasma level of EPI (ng/ml) was performed at one, two and three min during the 2 µg/kg/min EPI infusion for each anesthetic condition, and also at the time of appearance of arrhythmia (PLE). EPI infusions, beginning with 1 µg/kg/min, were spaced by 30-45 min intervals. The dose was doubled if arrhythmia did not occur. If arrhythmia occurred during the 8 ug/kg/min infusion, 6 µg/kg/min was also tested; if no arrhythmia occurred, then 10 ug/kg/min (maximum level) was infused. No animal received more than four EPI infusions and testing lasted < 3 hrs. Data for ADE and corresponding PLE were compared with permutation and student's paired t-tests.

Results. ADE's (µg/kg) and PLE's (ng/ml) for each test condition (Table) indicate that THIO reduced both the ADE and PLE with ENF ($p < .05$). With ISO, only one dog had arrhythmia, but six of eight did with ISO-THIO; thus, THIO facilitated arrhythmia with ISO ($p < 0.05$). However, ADE's and PLE's were greater with ISO-THIO than ENF-THIO ($p < 0.05$). There were no statistically significant differences between plasma EPI levels reached at one, two and three min during the 2 µg/kg/min EPI infusions with each anesthetic condition.

Discussion. Sumikawa and coworkers found an ADE of 21±4 µg/kg and PLE of 206±18 in dogs tested with ENF preceded by THIO induction (3). The higher value obtained in their study may be due to epinephrine tolerance(4). They used logarithmically spaced infusions beginning with 0.67 µg/kg/min, increased by $e^{0.2}$ amounts to reach the level of infusion (∼ 11 µg/kg/min, ∼ 14 successive infusions) producing arrhythmia. Also, only 10 minutes lapsed between infusions in their experiments. Plasma EPI levels during the 2 µg/kg/min infusion were similar for each test condition in this study. If this is true for higher infusion levels as well (these could not be tested with ENF-THIO because ventricular bigeminy or tachycardia occurred in all but one dog at EPI 2 µg/kg/min), then the THIO or ENF-THIO vs. ISO-THIO effect to facilitate EPI-induced ventricular arrhythmias is not due to an anesthetic - THIO interaction affecting plasma level of EPI. We can only speculate as to the cause for THIO potentiation of EPI-induced ventricular arrhythmias with inhalation anesthetics. It is known that THIO (5) and halothane (6) have contrasting effects on the action potential in ventricular muscle. As these affect action potential duration and repolarization, we postulate an interaction between THIO and anesthetics to produce alterations in the temporal dispersion of refractoriness between specialized conducting and working ventricular myocardial cells that favor reentrant ventricular arrhythmias.

TABLE. ADE's and PLE's* with Anesthesia (X±SE)

	N†	ADE	PLE
ENF	8	9.5±1.2	89.0±16.7
ENF-THIO	8	4.3±0.7	45.4±8.6
ISO	1	28.3	330
ISO-THIO	6	15.2±2.8	170±39

* Mayo Medical Laboratories, Rochester, MN

† N = Number of dogs with arrhythmia

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Title: METOCURINE ADMINISTRATION BY COMBINED BOLUS AND INFUSION

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Introduction. The neuromuscular blockade achieved by an initial dose of relaxant can be maintained with continous infusion of the relaxant at a rate matched to the elimination clearance of the drug. The rationale for the present bolus and infusion regimen of relaxant is based on the concepts of Mitenko and Ogilvie:[1] the bolus dose is calculated as the product of the desired plasma concentration and the distribution volume, while the infusion is the product of the plasma concentration and the elimination clearance.

Methods. The dosage regimen for metocurine was calculated from the data of Matteo and colleagues[2] (table 1).

Table 1

Desired plasma concentration	0.63 µg/ml
Distribution volume, V_{ss}	0.40 l/kg
V_d area	0.51 l/kg
Plasma clearance	1.07 ml/kg/min

The plasma concentration associated with 95% depression of twitch response should be obtained and maintained with a bolus dose of metocurine, 0.3 mg/kg, and an infusion of 0.04 mg/kg/hr, respectfully. The nine adults who gave institutionally approved written informed consent were scheduled for total hip replacement; they had no known renal or hepatic disease, and were between 62 and 76 years of age. Anesthesia was induced with thiopental, 3-4 mg/kg and maintained with ethrane, 0.7-1.5%, in a 50/50 mixture of nitrous oxide and oxygen. Ventilation was adjusted to maintain the end-expired carbon dioxide partial pressure between 30 and 40 mm. Following induction of anesthesia, the ulnar nerve was stimulated supramaximally at the wrist with a train-of four every 20s, and the hypothenar compound electromyogram (EMG) was recorded for 15-20 min. The bolus of metocurine was then administered and the infusion was commenced concomitantly. Plasma samples were obtained at -5, 2, 5, 10, 15, 20, 30, 45 and 60 min, and then at half-hour intervals during the infusion. The sampling schedule was recommenced in the postinfusion period, with additional samples at 1 1/2, 2, 4, 6, 8, and 12 hours. Urine volumes were collected half-hourly during the infusion and for the 24 hr after. Plasma and urinary aliquots were stored at -20C for later measurement of metocurine and creatinine concentrations. Metocurine concentrations were determined by an HPLC technique.[3] The pharmacokinetics of metocurine were obtained with the SAAM 23 nonlinear least-squares regression program.

Results. The metocurine infusion was continued for 2-3 hours. The initial peak associated with the bolus became less during the first hour, and a plateau in the plasma concentrations occurred during the second and third hours: at the end of the infusion the metocurine concentration was 0.65(±0.10) ug/ml. This was associated with 92(±8)% depression of the first twitch response. Spontaneous recovery from paralysis was minimal during the first half-hour after the infusion: at the end of a full hour there was 80(±12)% paralysis. Muscle relaxation in all patients was reversed easily with atropine and neostigmine at the end of the procedure.

Table 2. The Pharmacokinetics of Metocurine.

	Mean (SD)
Plasma concentration plateau	0.65(0.10) µg/ml
Distribution volume, V_{ss}	0.35(0.06) l/kg
V_d area	0.48(0.09) l/kg
Plasma clearance	1.33(0.18) ml/kg/min
Elimination half-life	240(49) min

Discussion. Tables 1 and 2 show reasonable agreement, despite differences in the techniques used, including dose administration, metocurine concentration determination and evaluation of the intensity of neuromuscular blockade. The pharmacokinetics reported for metocurine in "normal" patients in other studies show similar agreement,[2,4-6] suggesting that the regimen should be suitable for the majority of patients. These studies report mean values for V_{ss} between 0.35 and 0.42 l/kg and for V_d area between 0.45 and 0.58 l/kg; the mean clearance ranges from 1.07 to 1.85 ml/kg min, and the elimination half-life from 217 to 316 min. As there will always be subjects whose pharmacokinetics or pharmacodynamics differ from the norm, it may be neccessary to adjust the infusion according to the individual's responses to ulnar nerve stimulation.

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Title: EFFECT OF VECURONIUM ON INTRAOCULAR PRESSURE

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Introduction: Vecuronium, a new non-depolarizing muscle relaxant, has a rapid onset of action and minimal cardiovascular effects.(1) These properties may make it a useful muscle relaxant in patients with open eye injuries. However, a recent study has suggested that intraocular pressure (IOP) may increase following vecuronium administration.(2) Therefore, the purpose of this study was to examine the effects of vecuronium on IOP at short intervals after induction of anesthesia and tracheal intubation.

Methods: This study was approved by the Human Investigation Committee of the hospital and informed consent was obtained from all patients. Thirty patients (22 females/8 males) ages 14-67, weighing 40-109 kg (ASA Class I and II), scheduled for elective nonocular surgery, were divided into groups of 10 (Table). IOP was measured with a Mueller's electronic tonometer using a weight of 5.5 g, prior to and 15 seconds following induction. Vecuronium was injected immediately after the measurement of IOP was made. Thereafter the measurements were repeated at 90 seconds following vecuronium and 30, 60 and 120 seconds after intubation. Heart rate and blood pressure were recorded at the same intervals. The disappearance of the muscle twitch was noted with a peripheral nerve stimulator. The quality of intubation was subjectively assessed by vocal cord relaxation and the degree of coughing, bucking, or straining (if present) following intubation. All the patients were preoxygenated prior to induction and IOP measurements were performed in the supine position. Data for IOP was analyzed using two-way analysis of variance for repeated measures. The Newman-Keuls method was adapted for determining significance between means within groups. A one-way ANOVA was used to compare ages, weights, baseline blood pressures and heart rate. A $p < 0.05$ was considered statistically significant.

Results: The mean ages, weights, baseline heart rates and arterial pressure were not significantly different in the three groups. IOP fell significantly in all the groups 15 seconds following thiopental or etomidate (Figure). Following vecuronium administration in Group II, there was an additional significant decrease in IOP. Intraocular pressures were statistically lower at 60 and 120 seconds in Group II as compared to Groups I and III, and at 30 seconds as compared to Group I. All groups were significantly below controls at 2 minutes. Intubating conditions were judged unsatisfactory in Group I but satisfactory in groups II and III.

Discussion: Factors known to influence intraocular pressure such as hypoxia, hypoventilation, coughing, straining or the depth of anesthesia were minimized in the present study by adequate premedication, pre-oxygenation prior to induction and spraying of vocal cords with local anesthetic before tracheal intubation. The timing of IOP measurements was contrived to determine the changes in IOP following injection of each individual anesthetic agent, separately. The pronounced drop in IOP after higher induction doses of thiopental indicates that this may cause a suppressive effect of greater magnitude on ocular tension probably via the diencephalic center in the mid-brain. Increasing the dose of vecuronium from 0.1 to 0.14 mg/kg, which is reported to minimally affect the cardiovascular system, yielded improved intubating conditions. In conclusion vecuronium (0.1 to 0.14 mg/kg)was associated with a decrease in intraocular pressure. Therefore, vecuronium can be used safely to facilitate intubation in patients with open eye injury.

Table

Group I	T = 5 mg/kg, V = 0.1 mg/kg
Group II	T = 7 mg/kg, V = 0.14 mg/kg
Group III	E = 0.3 mg/kg, V = 0.14 mg/kg

T = Thiopental, E = Etomidate, V = Vecuronium

References:

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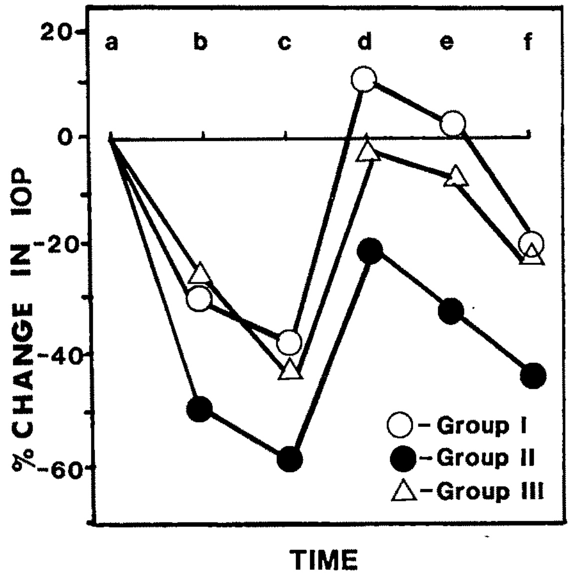
Figure: Changes in IOP following induction and intubation. a=baseline, b=15 sec post induction, c=90 sec after vecuronium, d,e,f=30, 60, and 120 sec after intubation.



Title: A NEW LOOK AT PRESSURE LOSS THROUGH ENDOTRACHEAL TUBES: RAE AND CAT TUBES

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Introduction. The pressure loss through an endotracheal tube (ETT) during spontaneous breathing has been the subject of several studies (1-4). Calculations and measurements for various breathing systems have shown that the pressure loss through the ETT is much greater than the corresponding losses through elbows, valves and other parts of the circuit (5). These losses may not be significant for healthy adults under anesthesia (3), but for infants and small children they can add substantially to work of breathing, leading to respiratory failure in some cases (2). Endotracheal tubes with pre-formed bends, such as RAE and CAT tubes, are now in common use in infants and children breathing spontaneously under anesthesia. Since tube curvature can increase frictional losses, particularly in the turbulent flow regime, it is worthwhile to determine the pressure losses through these curved ETTs at physiologic flow rates. This is the subject of the present study.

Methods. ETT diameters from 2.5 to 7.0 mm were studied. For each diameter a direct comparison was made between a straight ETT, an oral RAE, and a CAT tube. Steady gas flows (using air) were provided by an anesthesia machine using a calibrated orifice meter to determine flow rate. Pressure loss P through the ETT was measured with a water manometer having a resolution of 0.1 cm H20 (0.08 Torr). Each set of measurements was repeated using the same ETT, and then again using a different tube of the same specifications to check the manufacturer's consistency. Various empirical models that relate pressure loss and flow in tubes are used with the present data. These include simple power-law ($P = KQ^mR^n$) and polynomial ($P = K_LQ + K_TQ^2$) representations. The polynomial is intended to separate the contributions from the laminar ($K_L\,Q$) and turbulent (K_TQ^2) flow. The error in this model stems from the fact that the location of the transition between laminar and turbulent flow is itself a function of Q, and therefore the "constants" K_L and K_T will depend on Q.

Results. As in previous work by the present author (to be published), measured pressure losses through straight ETTs are 30-50% greater than those predicted by simple turbulent flow theory. This discrepancy is explained by the fact that the simplified theory is valid only for tubes of infinite length/diameter ratio, which is not the case for an ETT. The magnitude of the pressure loss for a spontaneously breathing infant is shown by the following example. For a 4.0 mm straight ETT and a peak flow of 150 cc/sec (a realistic value for "quiet" breathing) the measured P is 3.7 cm H_2O. This is the negative inspiratory pressure the infant must develop to breathe at his normal flow rate. For the more rapid breathing of a sick or stimulated infant, P will reach values greater than 10 cm H_2O very quickly. Fitting these data to the empirical models mentioned above shows the following. The power-law model yields a value for the exponent m of 2.03 ± 0.08 (mean ± SD) for flow rates in the turbulent regime. This is in good agreement with the theoretical value of 2.0. The exponent n for the tube radius dependence is -3.95 ± 0.12. (It is interesting that this exponent is in agreement with the "r to the fourth" law of Hagen-Poiseuille, which should be valid only for laminar flows.) The comparison of the RAE and CAT tubes with the straight ETTs yields very interesting results. For the smaller tube sizes (3.0 - 4.5 mm), the RAE tube consistently yields a 35-60% greater pressure loss than the corresponding straight tube at the same flow rate. The CAT tube has intermediate pressure losses, ranging from 10-30% greater than those of the straight tube. As ETT diameter increases above 4.5 mm, the differences between the three ETT types diminishes, until they produce virtually identical pressures at 6.0 mm diameter. If we use the polynomial model, $P = K_LQ + K_TQ^2$, we find that the constant K_L is nearly the same for the RAE and the straight ETT, whereas the values of K_T are much greater (35-60%) for the RAE tube. This is consistent with the idea that the increased resistance of the RAE tube is a result of its sharp bend, which will produce increased friction and hence pressure loss chiefly in the turbulent regime, where P is proportional to Q^2.

Discussion. The ventilatory response to increased airway resistance during anesthesia is highly variable, and pressure drops as small as 6 cm H_2O have produced at least temporary ventilatory failure, even in adults (3). We have shown that the pressure loss through the pre-formed oral RAE tube is significantly greater than the loss through a straight ETT for small diameter tubes. The CAT tube, on the other hand, has a much smaller increase in pressure loss relative to a straight tube, apparently due to its more gentle curvature. Therefore, a straight ETT should be used whenever possible in the spontaneously breathing infant. If a pre-formed curved tube is indicated, the newer CAT design is a better choice than the oral RAE, owing to its lower pressure loss.

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Title: THE EFFECTS OF CARBON MONOXIDE INHALATION ON NONINVASIVE OXYGEN MONITORING

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Introduction. Noninvasive monitoring of patient oxygenation during anesthesia is becoming standard practice in the operating room. Pulse oximeters and transcutaneous PO2 sensors provide continuous real-time data, and thus give early warning of impending hypoxia. These two noninvasive techniques measure distinctly different variables, hence each has its own advantages and disadvantages [1]. The pulse oximeter will not warn of impending danger until the arterial oxygen tension (PaO2) is low enough to cause significant desaturation. On the other hand, the transcutaneous PO2 (PtcO2) is dependent upon skin perfusion as well as PaO2 and thus requires more interpretation.

The pulse oximeter determines hemoglobin saturation (NSaO2) by measuring light absorbance at two wavelengths and comparing the ratio of the absorbances to a built-in calibration function. Because it senses only two wavelengths of light, the oximeter is in theory unable to differentiate oxyhemoglobin from other non-reduced species, specifically carboxyhemoglobin. The goal of the present study is to determine the accuracy of the pulse oximeter prediction of actual oxyhemoglobin (SaO2) in the presence of carboxyhemoglobin levels ranging from those of the heavy smoker (10-20%) to those of the burn victim (50-60%).

Methods. Five mongrel dogs were studied. Each dog was anesthetized with sodium pentobarbital, intubated, and ventilated at normocapnia. Monitoring included a femoral arterial line, Swan-Ganz pulmonary artery catheter, EKG, two Novametrics PtcO2 probes applied to shaved skin on the chest, and two pulse oximeter probes (Biox-III and Nelcor) applied to the tongue. FIO2 was varied from 0.12 to 1.0 at several levels of carboxyhemoglobin (COHb) for each dog. Each data set consisted of vital signs, cardiac output, PA wedge pressure, CVP, NSaO2, PtcO2, arterial blood gases (Radiometer model ABL-2), and arterial values of SaO2 and COHb determined by an IL-282 Co-Oximeter. COHb was varied slowly by adding carbon monoxide to the circle breathing system through a precision flow meter.

Results. First, the validity of using on dogs a pulse oximeter that was calibrated for humans must be verified. A plot of NSaO2 versus SaO2 without COHb, for FIO2 from 0.10 to 1.0, yields a slope of 0.92 and a correlation coefficient of 0.94 (standard error of estimate = 3%). Previous studies have shown similar correlations. Figure 1 shows both SaO2 and NSaO2 versus COHb level for an FIO2 of 1.0. The pulse oximetric NSaO2 shows little dependence upon COHb, while the actual SaO2 falls linearly with rising COHb (slope = -0.99, r-value = -0.98). In fact the sum of SaO2 and COHb is very nearly equal to NSaO2 for these data. The data at lower FIO2 show more scatter, but a similar relationship between NSaO2 and COHb. In contrast to this behavior, the relationship between transcutaneous PO2 (PtcO2) and PaO2 was unaffected by the presence of carboxyhemoglobin.

Discussion. It is clear from the data presented here that the pulse oximeter is unable to differentiate between oxyhemoglobin and carboxyhemoglobin. It senses either species as "saturated hemoglobin," since the light absorbance spectra of the two species are similar. The clinical implications of this are obvious. The burn victim with an acute inhalation injury may have a carboxyhemoglobin level of greater than 50%. This patient's oxyhemoglobin can then be no greater than 50%, yet the pulse oximeter may still read 100% (Figure 1). The heavy smoker with a COHb level of 10% may have an NSaO2 of 90% when his actual oxyhemoglobin is only 80%. In conclusion, the introduction of a non-reduced hemoglobin species other than oxyhemoglobin, such as COHb, can result in serious errors in oxygen saturation as determined by a pulse oximeter. The pulse oximeter should not be used to assess the oxygenation of patients with a suspected history of carbon monoxide inhalation. The transcutaneous PO2 continues to exhibit the same relationship with PaO2 either with or without carboxyhemoglobin.

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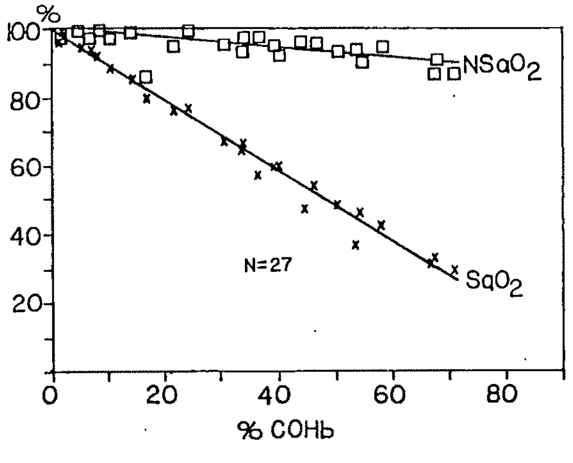
Figure 1. SaO2 and NSaO2 versus carboxyhemoglobin level, FIO2=1.0.



Title: ANESTHESIOLOGIST'S BACK: EPIDEMIOLOGY OF A MAJOR OCCUPATIONAL DISEASE

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Introduction. Previous studies have examined biological and chemical threats in the anesthesiologist's workplace. Physical hazards to anesthesia providers include both the dynamic strains of lifting or transferring patients and the more static stresses of poor posture maintained during patient monitoring. Low back pain (LBP) and radiculopathy are the most prevalent noninfectious occupational morbidities afflicting anesthesia providers at our institutions.

Methods. Abbreviated in Table 1, a back pain questionnaire was completed by the first 45 of 90 full-time clinical anesthesiologists encountered in our institutions' operating rooms. These 36 men and 9 women ranged from 25 to 60 years in age and from junior resident to full professor in anesthesia experience. The same questionnaire was completed by 160 of 600 non-anesthesiology clinicians contacted at our institutions. Control physicians consisted of the first 45 of the 160 responding clinicians who matched the 45 surveyed anesthesiologists on the basis of age, sex, and academic rank. Answers to questions and cumulative prevalences were tallied.

Results. Overall, 71% of the anesthesiologists had experienced back pain and/or radiculopathy, as had 42% of other physicians -- a highly significant difference in cumulative prevalence (see Table 2). Chronic LBP did not significantly differ in prevalence between the two groups. A statistically significant difference in cumulative prevalence was demonstrated between anesthesiologists and control physicians with respect to activity-limiting LBP ($p < .001$). This difference was reflected by matched pair analysis yielding an odds ratio estimate of relative risk of activity-limiting LBP for anesthesiologists 4.0 times that of non-anesthesiologists. Number of episodes of activity-limiting LBP correlated very strongly with age ($r=.57$, $p < .01$), strongly with years of anesthesia experience ($r=.42$, $p < .05$), and insignificantly with academic rank. Similarly, radiculopathy demonstrated a significant difference in cumulative prevalence between anesthesiologists and other physicians ($p < .001$). Mirroring this difference, the odds ratio estimated the relative risk of radiculopathy for anesthesiologists as 3.8 times that of non-anesthesiologists.

Discussion. For the anesthesiologists surveyed, 70% of activity-limiting LBP episodes were initiated or exacerbated on-the-job, yet less than 20% of these episodes were linked specifically to lifting patients. The majority of LBP episodes were ascribed to improper posture during monitoring or poor relaxation. A surprising number of anesthesiologists could associate their back troubles with specific job-related tasks, including the performance of endotracheal intubation and the place of central venous line. Psychological stress and muscle tension exacerbated these postures of vigilance and intervention. None of the anesthesiologists and only one of the control physicians noted involvement in litigation concerning their back. "Anesthesiologist's back" has had a major impact on our anesthesia as demonstrated by the full work-year of days missed by these 45 physicians. Only 3 of the anesthesiologists had received formal instruction on proper lifting and transferring of patients. Despite past nursing training on patient-lifting, our nurse anesthetists appear to have an even higher prevalence of LBP than our anesthesiologists. Growing evidence supports the theory that age-associated increases in LBP morbidity are exacerbated for anesthesia providers by their personal postures of vigilance and intervention and, to a lesser extent, by patient-lifting practices.

Table 1: Abbreviated Back Pain Questionnaire

1) List # of bouts of activity-limiting LBP.
2) Do you have chronic LBP?
3) List # of bouts of pain radiating to leg(s).
4) What activity initiated/worsened your LBP?
5) List # of times your LBP worsened at work.
6) How many workdays missed due to your LBP?
7) What home activities has LBP disrupted?
8) What therapy have you received for LBP?
9) Who taught you to lift/transfer patients?
10) Is any litigation pending about your LBP?
11) How do you limit your lifting or posture?

Table 2: Cumulative Prevalence of Morbidity

	Anesthesia M.D.'s (n=45)	Other M.D.'s (n=45)	Probability (Adjusted Chi-square)
Activity-limiting BP	25 (56%)	13 (29%)	p .001
Chronic LBP	14 (31%)	9 (20%)	N.S.
Radiculopathy	11 (24%)	3 (7%)	p .001
LBP and/or Radiculopathy	32 (71%)	19 (42%)	p .001

Title: CLONIDINE PROLONGS TETRACAINE SPINAL ANESTHESIA IN DOGS

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R3E 1X2

Introduction. Clonidine has been shown to stimulate both central and peripheral alpha$_1$ and alpha$_2$ adrenergic receptors. Following parenteral administration peripheral alpha$_1$ receptor stimulation produces a transient vasoconstriction[1], while following intrathecal administration a marked analgetic effect has been observed.[2,3] These pharmacodynamic properties may make clonidine a useful adjunct to spinal anesthesia. The present study was undertaken to assess the comparative efficacy of clonidine and epinephrine in prolonging tetracaine spinal anaesthesia in dogs.

Methods. Six mongrel dogs each weighing 17kg were studied using a radomized blind crossover design. Under thiopental-N_2O-O_2-isoflurane anesthesia, lumbar puncture was performed at the L_6-L_7 interspace with a #22 gauge spinal needle. Each animal received the following intrathecal solutions in 1ml 5D/W:

1) Tetracaine 4mg with clonidine 150µg
2) Tetracaine 4mg with epinephrine 200µg
3) Tetracaine 4mg
4) Clonidine 150µg
5) Epinephrine 200µg
6) 5% dextrose H_2O

Following intrathecal injection, N_2O-Isoflurane was discontinued and time to awakening was recorded. Sensory and motor function were assessed at 20 minute intervals for the 1st hour and 15 minutes thereafter. Duration of motor block was defined as the time from intrathecal injection to the time of standing unsupported. Sensory block was assessed by applying a 10 inch rubber-shod hemostat to the proximal one third of the shaved tail and moving it continuously during a 60 second application. Any reproducable purposeful movement was interpreted as a return of sensation. The data were analyzed using a completely randomized ANOVA. Multiple comparisons were performed where the effect was significant.

Results. The results are summarized in the table. The time from intrathecal injection to awakening was 19±2 minutes (mean±SEM), and did not differ significantly between the groups. The tetracaine with clonidine and tetracaine with epinephrine solutions produced motor blockade of similar duration. Both solutions produced a significantly longer duration of motor blockade than the plain tetracaine solution. No motor blockade was seen with the remaining solutions. Sensory blockade following the tetracaine with clonidine solution was significantly prolonged compared to the tetracaine, and tetracaine with epinephrine solutions. Clonidine solution alone produced a sensory block in all dogs, while only 1 dog receiving intrathecal epinephrine had a sensory blockade (40 mins). No neurological abnormalities were observed in any of the dogs.

Discussion. The results indicate that clonidine when used as an adjunct to tetracaine spinal anaesthesia is as effective as epinephrine in prolonging motor block, but significantly more effective in prolonging sensory blockade. The mechanism of the prolonged sensory blockade is unknown at present but may be related to a direct spinal cord, regional vascular, and/or general systemic effect.

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Duration of Blockade

Solution	Motor Blockade (mins.)	Sensory Blockade (mins.)
Tetracaine with Clonidine(N=6)	438±37**	323±31**
Tetracaine with Epinephrine(N=5)	402±63*	207±23
Tetracaine (N=5)	186±58	156±23
Clonidine (N=5)	0	76±17*
Epinephrine (N=6)	0	0+
5% Dextrose H_2O (N=6)	0	0

Values expressed as mean ± SEM
*P <0.05 compared to tetracaine group
**P <0.01 compared to tetracaine group
+One dog had sensory blockade - see results section

Title: FACTORS AFFECTING GAS ENTRAINMENT WITH HIGH-FREQUENCY JET VENTILATION

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Introduction. High-frequency jet ventilation (HFJV) involves two sources of gas: gas injected under high pressure and gas entrained by venturi effect. The entrainment of gas when HFJV is delivered proximally through an endotracheal tube was studied with a mechanical test lung. We determined the proportion of gas entrained in response to changes in drive pressure (DP), inspiratory time (T_I), injector size, injector position, positive end-expiratory pressure (PEEP), airway resistance (Raw), and lung compliance (C_L).

Materials and Methods. HFJV was provided by a solenoid-valve actuated ventilator (Healthdyne) with room air through a small-bore steel needle inserted into a swivel connector (Portex). The respiratory rate was 100 breaths/min throughout the study. The entrained gas was 9.87% CO_2. The gases were delivered via a regular endotracheal tube to a mechanical test lung (M II Vent-aid TTL) modified to include a mixing fan. The final CO_2 concentration in the test lung was measured by a capnograph (Godard). The proportion of gas entrained was determined from the formula: [% entrained gas] = ([final CO_2]/[entrained CO_2]) x 100. The baseline settings were DP of 20 psig, T_I of 20%, PEEP of 0 cm H_2O, a 14-ga injector positioned at the end of the connector, Raw of 5.5 cm H_2O/L/sec, and C_L of 100 cc/cm H_2O. Entrained gas was measured at 3 levels for each parameter while other parameters were kept at baseline settings (Table).

Results (Table). In the majority of the conditions studied, entrained gas represented 55% to 60% of the total amount of gas delivered to the test lung. No statistically significant differences in the proportion of entrained gas occurred with changes in C_L or PEEP. There were statistically significant differences in the amount of entrained gas at various T_Is, DPs, and injector positions, but these would probably not be clinically significant. Only injector size and Raw modified the proportion of entrained gas more than 5%. Entrainment increased with smaller injectors and decreased with higher Raw.

Discussion. The proportion of gas entrained when HFJV is delivered proximally via an endotracheal tube through a small-bore needle was found to be 55% to 60% of the total amount of gas delivered, which is similar to the 60% calculated from the data of Davey et al (1). Therefore, both sources of gas (jet and entrainment) must be considered when a problem such as humidification is addressed. As previously observed, the increased velocity of gas through the outlet of smaller injectors entrains more gas (2, 3). However, in dogs with normal and oleic acid-induced adult respiratory distress syndrome, a smaller injector resulted in inadequate gas exchange (4). The mechanism of gas exchange with HFJV is still unclear.

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TABLE. Percent entrained gas under 21 experimental conditions of high frequency jet ventilation delivered to a mechanical test lung

Parameter	Settings	Entrained Gas (%)
Drive pressure	20 psig	58.97 ± 0.58*
	30 psig	61.80 ± 0.60*
	40 psig	64.47 ± 0.65*
Inspiratory time	20%	58.97 ± 0.58†
	30%	60.38 ± 0.52†
	40%	59.72 ± 0.90†
Positive end-expiratory pressure	0 cm H_2O	58.97 ± 0.58
	5 cm H_2O	58.72 ± 0.72
	10 cm H_2O	58.97 ± 0.39
	15 cm H_2O	57.45 ± 0.67
Injector size	14 ga	58.97 ± 0.58*
	16 ga	67.32 ± 0.67*
	18 ga	75.00 ± 0.43*
Injector position	End-connector	58.97 ± 0.58*
	Mid-connector	54.03 ± 0.65*
	Endotracheal tube	56.03 ± 0.65*
Airway resistance‡	5.5 cm H_2O/L/sec	58.97 ± 0.58
	32.0 cm H_2O/L/sec	48.85 ± 0.45
	48.0 cm H_2O/L/sec	41.60 ± 0.85
Lung compliance	100 cc/cm H_2O	58.97 ± 0.58
	50 cc/cm H_2O	58.30 ± 0.52
	20 cc/cm H_2O	58.80 ± 0

Values are means ± SD.

*$p < 0.05$ by analysis of variance and Duncan's test and < 0.01 by unpaired *t* test compared with the control value.

†$p < 0.05$ by analysis of variance and Duncan's test compared with the control value.

‡Airway resistance was adjusted by using endotracheal tubes of smaller length and smaller internal diameter.

Title: LIDOCAINE ULNAR NERVE BLOCKS ALTER SSEP RESPONSES

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Introduction. Somatosensory evoked potentials (SSEP) have been used to examine the integrity of the brachial plexus.[1] This study compares the effects of saline and lidocaine infiltration of the ulnar nerve at the elbow, with and without epinephrine, on: a) the sensory visual analogue scale (VAS), and b) SSEPs recorded at the Erb's point, over the spine at C7, and over the sensory cortex.

Methods. Six healthy, unpaid, consenting volunteers had 4 modified ulnar nerve blocks;[2] 5 ml of each of the test solution was injected at 1-2 week intervals: a) preservative-free physiologic saline solution (PPPS), b) PPPS with 1:200,000 epinephrine, c) 1.5% lidocaine, d) 1.5% lidocaine with 1:200,000 epinephrine. In this institutionally approved, blinded study, the sequence of injection was randomized with a latin square design. The presence of sensory blockade was determined by pinching the fifth finger and the hypothenar eminence with a surgical clamp. The volunteers graded their degree of numbness with a VAS, 0 = no numbness, 10 = complete numbness. After baseline VAS scores were obtained, testing 30 minutes, then every 15 minutes until sensory recovery. if there was no sensory blockade at 30 minutes, testing continued for an additional half hour. A VAS score of 1 or less was considered a "no block" while a score of 8 or more was considered a "good block". This number was chosen because the volunteers stated, during the recovery of their local anesthetic block, that surgery would not be permitted on their fifth finger when the VAS score was 7 or below. The duration of "good block" (VAS score of 8 or more) was considered to be an index of useful local anesthetic effect. Using standard techniques, SSEP recordings were performed concomitantly with each sensory testing. Stimulating electrodes were placed over the ulnar nerve at the wrist and recording electrodes were placed at the ipsilateral Erb's point, over the spinal cord posteriorly at C7, and on the contralateral scalp over the sensory cortex. Amplitude and latencies of the composite responses from all 3 recording sites were monitored and recorded. After each injection, the SSEP response was considered to be abnormal when the following changes occurred for 15 minutes or more: a) decrease in amplitude by 50% or more,[3] b) increase in latency by 15% or more. The duration of each abnormality and altered sensory VAS score ≥ 8 was noted for each injection. With the duration of VAS score of ≥ 8 as the dependent variable, multiple linear regression (MLR) analysis was used to select which of the 6 SSEP criteria adequately predict the variable.

Results. Using the VAS scores, all the saline and saline with epinephrine injections resulted in "no block", while all the lidocaine and lidocaine with epinephrine injections were followed by "good blocks". The duration of "good block" was 76 ± 22 minutes with lidocaine and 224 ± 65 minutes with lidocaine with epinephrine. The 6 SSEP measurements (latency and amplitude at all 3 sites) gave on false positives, i.e. no abnormalities with "no block". For "good blocks", all the amplitude measurements showed changes of response (depression over 50%) with the exception of cortical measurements in one subject after a plain lidocaine injection. Similarly, there were increased latencies at Erb's point and C7 with lidocaine blocks. In contrast, change in cortical latency was seldom seen. Variable selection by MLR analysis of the SSEP measurements gave a statistical model that sensory block duration (VAS ≥ 8) could be specified by the duration of the reduced C7 amplitude ($R^2 = 0.93$).

Discussion. The lack of changes in the SSEP amplitude and latency, and in the VAS scores, showed that epinephrine does not have a local anesthetic effect on the ulnar nerve. This contradicts the reported finding of segmental hypalgesia from T10 to L2 for 6 hours after epidural administration of 50 μg epinephrine in 10 ml saline.[4] The difference in results is probably due to the lack of influence of the descending supraspinal noradrenergic pathways on a peripheral nerve setup. We also showed that the duration of depression ($\geq$ 50%) of the C7 amplitude of the SSEP provides an objective index of the duration of useful sensory blockade of the ulnar nerve.

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Title: DOES TOPICAL ANESTHESIA OF THE SPHENOPALATINE GANGLION WITH COCAINE OR LIDOCAINE RELIEVE LOW BACK PAIN?

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Introduction. Sphenopalatine ganglion block has been advocated for relieving muscle spasm, neuralgia, vasospasm, reflex sympathetic dystrophy, and low back pain (1). In a double blind study, we compared the duration of action and the efficacy of sphenopalatine ganglion block with cocaine, lidocaine, or a placebo to relieve chronic low back pain.

Materials and Methods. The protocol was approved by the committee on human experimentation. Twenty-one patients (aged 21-70 years) with chronic low back pain unrelieved by most acceptable surgical and nonsurgical methods were selected for study. Either normal saline, 10% cocaine, or 4% lidocaine (Xylocaine) was topically applied to the sphenopalatine ganglion by placing a pledget soaked with one of the solutions on an applicator and passing it bilaterally along the inferior and middle turbinates of the nose until contact with the sphenoid bone. The pledgets were left in place for 30 min. Each patient was treated in the morning and the afternoon on 2 consecutive days for a total of 4 treatments. The degree of pain was determined by asking the patient to judge it on a scale of 0 (no pain) to 10 (the worst pain the patient had experienced). Pain was evaluated before the first treatment; 1 hr after the second treatment and 1 hr after the fourth (last) treatment; and 1 day after, 1 week after, and 1 month after the last treatment. For each time period, data were analyzed by the Kruskal-Wallis test for statistical differences between the median responses to the treatments and, for each drug, by the Wilcoxon signed rank test for any differences in pain before the block compared with any time after the block.

Results. Analysis of baseline pain scores showed that pain did not differ between treatment groups, thus comparison of the groups was valid. At 1 week, treatments differed statistically ($P = 0.0260$). Cocaine and lidocaine did not differ in effectiveness. Saline at 1 week had a higher median response (gave less pain relief) than either cocaine ($P = 0.0594$) or lidocaine ($P = 0.0256$). No patient had statistically significant pain relief with saline. At 1 month, treatment groups did not differ statistically ($P = 0.07$). Only 4 out of 15 patients who had the sphenopalatine ganglion anesthetized with a local anesthetic had a decrease in pain rating of more than one point, not significantly different from the 1 out of 7 control patients. No other differences were found between the treatments at the other time points. Data from before the block were compared with those afterward to determine when the treatment started to take effect. The actual permutation distribution of the statistic was generated for each time period because the sample sizes were small and ties were present (if pre- and post-treatment scores were the same); no statistical differences were found at the 0.05 level, therefore, the exact time when pain relief began could not be determined.

Discussion. Sphenopalatine ganglion block was judged by approximately half the patients in this study who received either cocaine or lidocaine to have decreased the intensity of pain at 1 week. Whether the block was performed with 10% cocaine or 4% lidocaine made no difference in the effect of the pain relief. Though clinical pain relief started after the last block, statistical significance did not occur until 1 week after the last treatment. Long-lasting pain relief, i.e., 1 month after treatment, was poor. The mode of action of the block has been postulated to occur via the autonomic ganglion. The brief duration of relief limits the use of this block in chronic pain patients. Why pain relief is not maximal immediately after the block requires further investigation.

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Table. Relief of Low Back Pain Scored on a Scale of 0 (No Pain) to 10 (Worst Pain Experienced) After Sphenopalatine Ganglion Block With 10% Cocaine, 4% Lidocaine, or Saline

	Pain Score					
	Before	After Drug				
Drug	Drug	1 h	48 h	1 day	1 wk	1 mo
Cocaine ($n = 7$)	2	2	7	7	2	2
	5	2	2	1	1	6
	5	3	0	0	1	4
	5	5	1	3	5	5
	5	5	4	5	5	4
	7	0	3	2	2	4
	10	10	10	10	10	10
Lidocaine ($n = 7$)	3	3	1	3	3	3
	4	6	5	5	5	5
	7	7	7	4	1	2
	7	9	4	8	8	ND*
	8	4	6	1	6	7
	8	8	10	10	5	5
	10	0	1	0	1	10
	10	5	3	3	2	2
Saline ($n = 7$)	5	5	2	7	8	8
	6	6	3	3	6	6
	7	7	7	7	7	10
	8	7	0	3	5	5
	8	8	8	8	8	8
	9	9	3	10	10	10
	9	9	10	10	10	10

*Not determined because patient received an epidural steroid injection.

Title: COMPARATIVE RIGHT VENTRICULAR FUNCTION DURING ASSIST CONTROL, INTERMITTENT MANDATORY AND SPONTANEOUS VENTILATION.

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Introduction. The output of the right ventricle is significantly afterload dependent. Principal ventilatory determinants of right ventricular afterload (pulmonary vascular resistance) are airway pressure and resting lung volume.[1] Total pulmonary vascular resistance (PVR) is increased when lung volume is either decreased or increased from a normal functional residual capacity (FRC). Increases in transpulmonary pressure during mechanical inspiration increases lung volume and exponentially increases PVR. Changes in ventilatory phase or mode may, therefore, modulate right heart hemodynamics by causing alterations in transpulmonary pressure gradients and PVR. This study evaluates right ventricular pump function (RVEF), right ventricular end-diastolic volume (RVEDV), right ventricular end-systolic volume (RVESV) and PVR during assist control (AC), intermittent mandatory (IMV) and spontaneous (SV) modes of ventilation.

Methods. In accordance with an approved Human Investigation Committee protocol, ten (n=10) postoperative ventilated patients were evaluated. Mechanical ventilation was maintained at constant tidal volume (mean = 12 cc/kg), F_IO_2 (mean = .4), respiratory rate (normocapneic), and positive end-expiratory pressure (mean = 5 cmH_2O), while ventilatory modes were varied between AC, IMV and SV. Hemodynamic measurements recorded at end-exhalation included: heart rate (HR), mean arterial blood pressure (MAP), right atrial pressure (RAP), right ventricular end diastolic pressure (RVEDP), pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP). RVEF, RVEDV, RVESV and cardiac output (CO) were calculated from diastolic washout plateaus obtained from a rapid response thermistor (50 msec) tipped Swan Ganz catheter.[2]

Analysis of data was performed using one way analysis of variance (Mean ± SD) and coefficient of correlation; $p < .05$ considered significant.

Results. Significant changes were observed in PVR during AC, IMV and SV. PVR was maximal during AC, intermediate during IMV, and minimal during SV. Changes in PVR were directly related to changes in RVEDV and RVESV; and inversely related to changes in RVEF. (Table I).

RVEDP increased in direct relation to PAP between AC, IMV and SV. Left ventricular preload (PCWP), HR, and CO remained constant during all modes of ventilation. (Table II).

Conclusions.

1. Increase in afterload on the right ventricle causes a decrease in RVEF, and a concomitant increase in RVEDV and RVESV.
2. The dependency of RVEF on afterload is demonstrated by ventilatory-induced changes in right ventricular hemodynamics and thermal ejection fraction.
3. Right ventricular function was most impaired during AC ventilation and recovered with increasing levels of negative inspiration during IMV and SV.

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Table I

MODE	RVEF (%)	RVEDV (cc)	RVESV (cc)	PVR (dyne cm^5/s)	CO (l/m)
AC	29±7	312±123	197±70	176±53	7.7±3
IMV	42±10*	231±87	135±59*	137±36*	9.2±5
SV	47±11*	196±74*	117±49*	52±39*	9.2±7

Table II

MODE	HR (b/m)	RAP (mmHg)	RVEDP (mmHg)	PAP (mmHg)	PCWP (mmHg)
AC	99±19	11.0±6	14.5±8	27±8	13.5±6
IMV	98±15	7.5±3	9.1±7	17±5*	12.5±5
SV	95±18	4.5±3*	6.0±2*	16±7*	10.5±4

$p < .05$ as compared to AC mode

Title: NALBUPHINE PRODUCES SIDE-EFFECTS WHILE REVERSING NARCOTIC-INDUCED RESPIRATORY DEPRESSION

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Introduction: High dose narcotic anesthesia improves hemodynamic stability during surgery and provides excellent postoperative analgesia. The associated respiratory depression necessitates the use of mechanical ventilation in an intensive care unit (ICU) for 24-48 hours following surgery. Such respiratory depression can be reversed by naloxone, a medication which can also reverse the analgesia and produce hypertension, dysrhythmias, and pulmonary edema (1). Nalbuphine, a partial agonist-antagonist narcotic has been reported to be effective in reversing respiratory depression following narcotic administration while retaining the level of analgesia (2,3).

The present study was designed to examine the ability of nalbuphine to reverse fentanyl-induced respiratory depression, thus allowing earlier termination of mechanical ventilation.

Material and Methods: Institutional Review Committee approval of the protocol and informed patient consent were obtained. Nine males and one female were studied. Their ages ranged from 46 to 76 years with a mean of 63±8 years. All underwent major abdominal vascular surgery. Anesthesia was induced with diazepam and fentanyl, the latter being administered to a total dose of 50-75 µg/kg. Maintenance of anesthesia was achieved with nitrous oxide in oxygen and isoflurane. Pancuronium was the muscle relaxant.

In the ICU, hemodynamic stability was determined in terms of cardiac index, systemic arterial pressures, heart rate, and pulmonary arterial and wedge pressures. Respiratory function was measured by arterial blood gas analyses, respiratory rate, end-tidal carbon dioxide percentage (ET_{CO_2}), and the pressure generated in the first portion of the inspiratory phase ($P_{0.1}$ sec). These measurements were made during the assist/control (AC) mode of mechanical ventilation, and repeated after a change to an intermittent mandatory mode (IMV) of 2 breaths/minute. In the randomized control group of 6 patients, the AC mode was reinstituted when the ET_{CO_2} reached 7% of the expired gas or if there were any signs of hemodynamic instability. In the study group, nalbuphine was administered intravenously (0.3 mg/kg--first two patients (3), 0.1 mg/kg in third patient, 0.025 mg/kg in fourth patient) as soon as the patient had stabilized on an IMV of 2 breaths/minute. Following nalbuphine, patients were either placed on continuous positive airway pressure for at least 30 minutes prior to tracheal extubation or were returned to the AC mode until the following day. Statistics were by Student's "t" test for paired and unpaired values as appropriate with P<0.05 considered significant.

Results: All patients had sufficient respiratory depression on arrival in the ICU to prevent tracheal extubation on the day of surgery. The control group underwent extubation on the day after surgery.

Before the administration of nalbuphine, the measurements of cardiac and pulmonary function did not differ statistically between the control and study groups. After administration of nalbuphine there was reversal of respiratory depression (Table) but all patients became agitated, experienced pain within minutes of receiving the medication, and all required further doses of a narcotic. The first and second patients experienced nausea and the second vomited. The third patient became severely confused and required postoperative psychiatric support. The third and fourth patients underwent tracheal extubation on the night following surgery while the first two were kept sedated and mechanical ventilation continued because of the occurrence of dysrhythmias. One control patient had a documented subendocardial infarction in the postoperative period.

Discussion: The results of this study show that nalbuphine is effective in reversing the respiratory depression induced by a large dose of fentanyl. However, the effects on other systems are not acceptable, particularly in a group of patients who may already be at risk for myocardial ischemia. Despite the slow administration of nalbuphine in recommended small doses (3), the production of pain and the occurrence of hypertension, tachycardia, and dysrhythmias were very reminiscent of similar effects seen following the administration of naloxone (1). Because our experience is different from that already reported in the medical literature regarding nalbuphine, we feel that, for reversal of narcotic-induced respiratory depression, particularly in patients at risk for myocardial ischemia, this agent cannot be freely recommended. Before this application of nalbuphine can be supported, further studies are needed to define dosage, rate of infusion, patient population, and relationship to reversal of different narcotics.

	Nalbuphine Group		
	Before	After	
Table	(mean ± S.D.)		P
Respiratory Rate (per min)	10 ± 1	23 ± 2	<0.001
ET_{CO_2} (%)	7.0 ± 0.3	5.6 ± 0.7	<0.01
$P_{0.1sec}$ (mmHg)	4.0 ± 1.4	13.0 ± 2.6	<0.001
Heart Rate (per min)	70 ± 10	84 ± 2	<0.05
Systolic Blood Pressure (mmHg)	139 ± 29	177 ± 24	<0.001
Diastolic Blood Pressure (mmHg)	81 ± 15	94 ± 14	<0.001

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Title: ISOFLURANE ATTENUATES EPICARDIAL CORONARY ARTERY RESPONSE TO PHENYLEPHRINE AND $PGF_{2}\alpha$ IN DOGS

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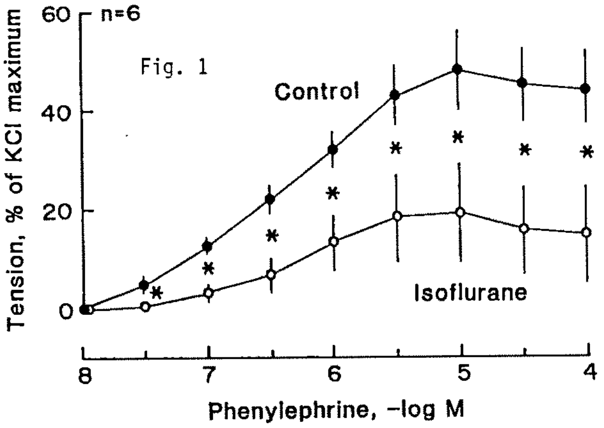
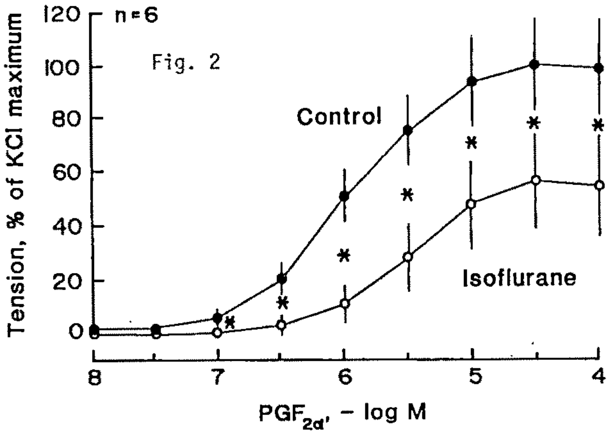
Introduction. Normal epicardial coronary arteries are thought to have little underlying vascular tone, while in coronary artery disease vascular tone is thought to be elevated and to contribute to the degree of narrowing of atheromatous lesions.[1] Although isoflurane has little effect upon normal epicardial coronary arteries in the dog,[2] its effects in the presence of increased vascular tone are unknown. This study was designed to determine whether or not isoflurane could prevent spastic contraction of large coronary vascular smooth muscle.

Methods. Four millimeter long rings of circumflex and left anterior descending coronary arteries were removed from dogs anesthetized with sodium pentobarbital. They were placed in an organ chamber filled with modified Krebs-Ringer bicarbonate solution at 37°C, connected to a strain gauge for measurement of isometric force, maintained at their optimal length-tension relationship, and aerated with a 95% O_2-5% CO_2 gas mixture.[3] Isoflurane from an anesthetic vaporizer was added to the gas mixture and its concentration was measured with a Beckman LB2 analyzer. Concentrations in the bath itself were measured by gas chromatograph. Vascular ring tension was measured in the resting state and following increasing concentrations of KCl, phenylephrine, and prostaglandin $F_{2}\alpha$ ($PGF_{2}\alpha$) both in the presence and absence of 2.3% isoflurane. Potassium, phenylephrine and $PGF_{2}\alpha$ were introduced into the bath with a micropipette. Data was represented as percent of maximum response to 40 mEq KCl. Paired t-test ($p < 0.05$ being significant) was used to analyze the data.

Results. Isoflurane 2.3% (1.5 MAC in the dog) had neither an effect on basal coronary artery tension nor upon vasoconstriction produced by potassium ions. Isoflurane reduced the vasoconstrictor response induced by phenylephrine and by $PGF_{2}\alpha$. In Figures 1 and 2, tension generated by the coronary segment was plotted against bath phenylephrine and $PGF_{2}\alpha$ concentration during control conditions and in the presence of isoflurane. Isoflurane significantly reduced the tension generated by increasing concentrations of phenylephrine and $PGF_{2}\alpha$ ($p < 0.05$ to $p < 0.005$).

Discussion. Isoflurane attenuated large coronary smooth muscle spastic contraction induced by phenylephrine and $PGF_{2}\alpha$ in the dog. This effect has clinical implications. In man the balance between endogenous coronary dilator and constrictor influences is probably disturbed in coronary artery disease and an abnormal, constrictor response may predominate in atheromatous regions of coronary arteries.[1] The severity of coronary obstructions depends not only upon size of the atheromatous lesion but also upon underlying coronary tone. If isoflurane attenuates the response to vasoconstrictor stimuli in man, it may improve blood flow through coronary stenoses in both classical and Prinzmetal's angina. It remains to be determined whether or not isoflurane also attenuates the vasoconstrictor effect of other mediators such as thromboxane A_2 and seratonin released during platelet aggregation.





Figs. 1 and 2. Tension developed by coronary rings obtained from six dogs (mean ± SEM) following exposure to phenylephrine (Fig. 1) and $PGF_{2}\alpha$ (Fig. 2) during control conditions and following isoflurane administration (2.3%, 1.5 MAC). * $P < 0.05$ to $P < 0.005$.

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Title: POST LUMBAR PUNCTURE HEADACHE IN PEDIATRIC ONCOLOGY PATIENTS

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Introduction. In adults, the syndrome of Post lumbar puncture headache (PLPHA) is a well-known, common and frequently vexing problem. In contrast, there is a paucity of literature discussing PLPHA in children. Several pediatricians have reported that few, if any, children experience PLPHA (1,2). However, these claims were apparently made after retrospective chart review or on the basis of a "clinical impression." Therefore, pediatric oncology patients who required lumbar puncture were prospectively studied to determine the incidence of PLPHA in a pediatric population.

Methods. Subjects were 26 children, aged 3-17, who were referred to the Pediatric Oncology Department. They required lumbar puncture for initial diagnosis, follow-up of treatment, or for intrathecal instillation of chemotherapeutic agents. 22 of the children were diagnosed as having acute lymphoblastic leukemia; the others had acute myelocytic leukemia or non-Hodgkins lymphoma.

Lumbar puncture was usually followed by bone marrow biopsy; both procedures were performed under general anesthesia (3). All lumbar punctures were accomplished with a 20 gauge needle, with removal of 1-2 cc's of cerebrospinal fluid.

Anesthesia was induced with intravenous methohexital 3 mg/kg, and was maintained with mask inhalation of nitrous oxide 70% in oxygen with enflurane 1-3%. In all cases, anesthesia was required for less than 10 minutes.

The nature of the investigation was explained to the children's parents, who all agreed to participate. They were asked to fill out a questionnaire daily for 5 days, commencing on the day of the lumbar puncture. The form contained questions regarding the presence of a headache, whether it was postural in nature, and whether there was associated nausea, vomiting, sleepiness or neck pain. A stamped, addressed envelope was provided so that the form could be returned by mail. A reminder was subsequently mailed to the parents to ensure that all forms were returned.

The data were evaluated by chi square analysis.

Results. Parents of 22 of the 26 children returned the questionnaires. Since many of the children were studied on more than one occasion, questionnaires regarding 36 lumbar punctures were evaluated.

The data are presented in Table 1. Postural headaches occurred significantly more often in children over the age of 13 than in those who were 12 or less. These headaches usually lasted less than 48 hours. However, one 14 year old boy had a postural headache that lasted 72 hours, while a 17 year old girl had a severe postural headache that lasted 5 days. She was the only patient who experienced any neck pain following lumbar puncture.

Discussion. These data indicate that PLPHA does occur in children aged 13 and over, an age that coincides with the beginning of adolescence. It appears to be rare in younger children: only one mild PLPHA was observed among the 17 children who were under the age of 13.

Others (4) have speculated that the lower intracranial pressure of children (5) protects tham from prolonged CSF leakage through the dural puncture site and hence, from PLPHA. It would be of interest to determine whether CSF pressure measured at the time of the lumbar puncture predicts subsequent PLPHA. Measuring CSF pressure in this investigation would not have been meaningful because of the confounding influence of anesthetic drugs, coughing and breath holding during the procedure, possible presence of CNS leukemia, etc.

It is possible that the response of pediatric oncology patients to lumbar puncture reflects the uniqueness of their disease and its treatment. Thus, conclusions drawn from these data need confirmation by studies in other pediatric populations. However, studying pediatric oncology patients has at least two advantages 1) the diagnoses are relatively uniform and 2) most of these patients are ambulatory.

In summary, the data obtained in this study suggest that PLPHA can occur in the pediatric age group. Because the risk of this complication rises sharply with adolescence, pediatricians should especially consider using small spinal needles in children over the age of 12.

TABLE 1

	ages 3-12	ages 13-17
average age of child studied	7.6	15.2
total # of lumbar punctures	27	9
# of PLPHA's	1	7
# without PLPHA's	26	2

$X^2 = 17.3, \quad P < 0.001$

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Title : EFFECTS OF CHRONIC ADMINISTRATION OF VERAPAMIL ON CARDIAC ELECTROPHYSIOLOGY IN THE RABBIT

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Introduction. Verapamil (V) is a lipophilic calcium blocker which accumulates in the myocardium[1]. The possibility that chronic administration of V may produce relatively high myocardial concentrations must be considered when evaluating its pharmacologic effects. We therefore investigated the effects of chronic administration of V on cardiac electrophysiology in the rabbit.

Methods. 7 New Zealand rabbits were treated for 30 days with V (1 mg/kg IP b.i.d.). Another group of 7 rabbits were injected with saline (S). After 30 days blood samples were taken and the animals were sacrificed and their hearts immediately placed in oxygenated Krebs solution. The SA node was removed from V- and S-treated rabbits and mounted in pair in a tissue bath, superfused with a 97% O_2 - 3% CO_2 mixture and maintained at 37°C (pH 7.4). Membrane potentials (MP) were simultaneously recorded from both nodes. The effects of epinephrine (EPI 0.1-20 µg/ml) and acetylcholine (ACh 0.18-18.0 µg/ml) were studied . Similarly papillary muscles were taken from the right ventricles and paced at 30,60,75 & 100 BPM. In addition, the effect of EPI (0.05-0.2 µg/ml) was also examined. The plasma and myocardium were analyzed for V and norverapamil (NV). HR and contractile force (CF) responses were compared using the paired t-test.

Results. V-treated SA nodes showed a lower spontaneous rate of discharge (Fig. 1) as compared to the control (183 vs 202 BPM). V-treatment significantly attenuated the chronotropic effects of EPI, while the effects of ACh were enhanced (p<.05). Peak CF was lower at all HR in V-treated papillary muscles (Fig. 2), although the positive staircase affect is still present. Response to EPI is also depressed (Fig. 3). MP's and APD_{50} were not significantly different, while dV/dT of the phase 0 was depressed from 67 to 55 V/s. Plasma samples obtained 14 hours after the last dose of V contained no detectable amounts of V and NV. The myocardial tissue contained 6.9±1.2 ng V/gm and no NV.

Discussion. The results show that chronic treatment of rabbits with V alters their inotropic and chronotropic responses to adrenergic as well as cholinergic stimuli. The data suggest that following the chronic treatment, NV does not contribute to the observed effects. It is not clear if these effects are due to a chronic exposure to V or due to the small amounts of V present in the tissue. If the latter is the cause, clearly the threshold concentrations producing these effects are very low (in the range of 3.0 to 10.8 ng/gm), and that the plasma concentrations are not indicative of the tissue levels of V.

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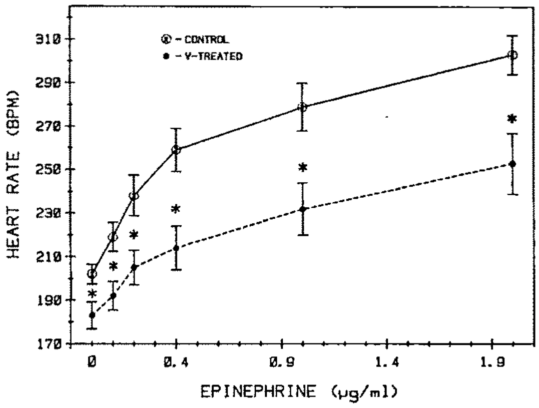

Figure 1. *P ≤ 0.05 vs. Control

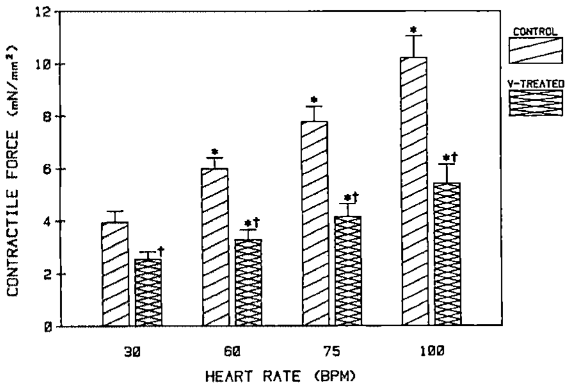

Figure 2.

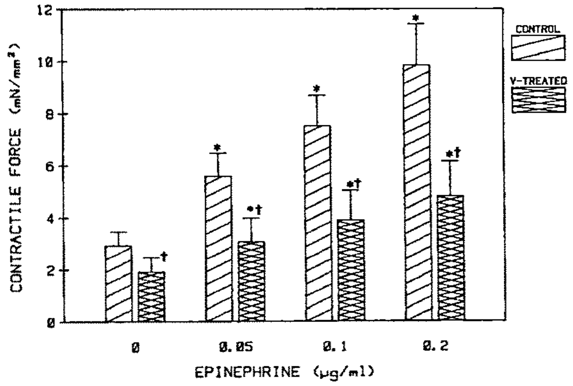

Figure 3. *P ≤ 0.05 vs. 0 µg/ml
†P ≤ 0.05 vs. Control

Title: CARDIOVASCULAR EFFECTS OF ATRACURIUM AND VECURONIUM ON DIGITALIZED DOGS

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Introduction. Atracurium (ATR) and vecuronium (VEC) are two shorter-acting, non-depolarizing muscle relaxants recently introduced into clinical practice. The potential therapeutic advantages offered by these new drugs in patients with poor cardiovascular function are the following: 1) the absence of cumulative effects from repeated doses because of rapid elimination pharmacokinetics, and 2) reported to have minimal cardiovascular side-effects. Since many of these patients may be receiving digitalis therapy at the time of surgery, a significant effect of these new drugs on digitalis-induced arrhythmias would be of great interest to anesthesiologists. The purpose of this study was to examine the effects of ATR and VEC on a model of digitalis-induced arrhythmias in dogs.

Methods. Thirty dogs were anesthetized with pentobarbital, 35 mg/kg, intubated, and mechanically ventilated with 100% O_2. Ventilation was adjusted so that $PaCO_2$ was 35 ± 2 mmHg. Catheters were placed in the femoral artery and vein to record blood pressure, for drug infusions, and to obtain blood samples for arterial blood gas and electrolyte analysis. A standard ECG lead II and blood pressure were monitored continuously on an oscillographic recorder. After a 45 minute stabilization period, the animals received a constant I.V. infusion of ouabain, 35 mcg/kg, using an IMED infusion pump. The dogs were then divided into two groups; one group received ATR, 1.0 mg/kg and the other group received VEC, 0.2 mg/kg. The first bolus injection was given three minutes after the start of significant ventricular ectopy. After 10 minutes, a second injection of the drug was given and the ouabain infusion was discontinued. If normal sinus rhythm (NSR) did not return after 10 minutes, a KCl infusion was administered until NSR was observed or a stable rhythm was established. The KCl was discontinued and a third dose of either VEC or ATR was administered.

Results. The mean dose of ouabain required to produce ventricular ectopy was 66.6 ± 2.9 (mean ± SE) mcg/kg. There was no change in the rate of ventricular ectopy or in the morphology of the premature ventricular contractions as a result of the injection of either ATR or VEC. If NSR was present at the time of injection or after KCl infusion, this rhythm was not altered by either drug. The ouabain infusion increased systolic blood pressure from approximately 150 mmHg to 200 mmHg; blood pressure transiently (less than 5 min) decreased by 33 ± 7 mmHg after the first injection of ATR and by 24 ± 4 mmHg after the second ATR injection. In the second group, the decrease in systolic blood pressure was less than 20 mmHg after VEC.

Discussion. The results of this study indicate that ATR or VEC may be administered to a fully digitalized heart without causing adverse effects on rhythm or disturbances in conduction. In addition, neither drug, when given a second time, increased ouabain toxicity or prevented KCl conversion to NSR. In contrast, pancuronium and succinylcholine have been shown to increase arrhythmias in patients receiving digitalis.[1,2]

In conclusion, these observations suggest that therapeutic doses of either ATR or VEC may be administered to patients receiving digitalis without significant increases in arrthymogenicity.

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Title: "CORONARY HEMODYNAMIC EFFECTS OF NIFEDIPINE DURING ISOFLURANE ANESTHESIA IN THE DOG"

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Introduction. Nifedipine (N), is a calcium channel blocker that has peripheral as well as coronary vasodilating effects. Interactions with N and volatile anesthetics remain in the field of investigation. In halothane (1%) anesthetized dogs a single intravenous dose of N resulted in a decrease in mean arterial pressure (MAP) with a significant tachycardia.[1] Isoflurane (F), a volatile anesthetic with peripheral[2] and coronary vasodilator effects in dogs causes an increase in heart rate (HR). This study was designed to investigate the plasma level related interactions of N on coronary hemodynamics during F anesthesia in the dog to determine if the reduction in MAP and increase in HR associated with N adversely affect global myocardial oxygenation.

Methods. Seventeen dogs weighing 23 ± 1 kg (mean ± SEM) with chronic tracheostomies were anesthetized with F in 40% O$_2$ in air. Mechanical ventilation controlled PaCO$_2$ at 35.0 ± 0.9 mmHg (arterial pH 7.37 ± .01). Maintenance of anesthesia was by F 1.78 ± 0.03% end tidal (mass spectrometry); vol% in blood 1.21 ± 0.4%. Electrocardiogram lead II at fast paper speed for measurement of PR interval; femoral arterial pressure for MAP and diastolic arterial pressure (DAP); left ventricular LV dP/dt (Millar catheter); and right atrial (RA), pulmonary artery mean (PAM) and capillary wedge pressures (PCWP), from a PA catheter were continuously recorded. Cardiac outputs (CO) were determined by the Fick method, and cardiac index (CI), stroke volume (SV), pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR) were calculated. A Webster thermodilution coronary sinus catheter was introduced aided by fluoroscopy. Total coronary sinus blood flow (CSBF) was measured by thermodilution in duplicate, and coronary vascular resistance (CVR) was calculated. Arterial (art), mixed venous and coronary sinus (CS) blood samples were obtained simultaneously for blood gases and oxygen content. Art and CS samples were also drawn for lactate (L), plasma levels of epinephrine (E) and norepinephrine (NE). N plasma levels were drawn and assayed by high performance liquid chromatography. Myocardial oxygen consumption (MVO$_2$) and myocardial lactate extraction ratio (MLER) were computed. Following hemodynamic stabilization for 1 hour on F and measurement of control values, the animals were divided into three groups. Group I (n=6) served as a control group and received F for 30 min. The subsequent groups were randomized where group II (n=5) received a loading dose of N, 10 µg/kg/2 min, followed by N 2.5 µg/kg min, for 30 min. Group III (n=6) received a loading dose of N 20 µg/kg/2 min, followed by N 5.0 µg/kg/min for 30 min. Measurements were made in group I at 30 min and in groups II and III at 2, 20 and 30 min during the infusion. All experimental procedures involving N were carried out under gold fluorescent light because of the susceptibility of this compound to photodegradation. All data were evaluated by analysis of variance for repeated measures with Bonferroni t-tests. $P<0.05$ was considered statistically signficant.

Results. There were no changes in any variable in group I. Values at 20 and 30 minutes were equivalent for groups II and III. N levels achieved in group II were 26 ± 5 ng·ml^{-1} and in group III 57 ± 9 ng·ml^{-1}. Coronary hemodynamics; myocardial metabolic variables; art NE; and systemic hemodynamics are listed in Tables I and II for control and 30 minute values. There were no significant changes in RA, PAM, CI, SV, PVR, PR interval or E in the three groups at any time. PCWP rose after the N loading dose in group II and returned to control values at 20 min post infusion (data not shown). In group II CSBF, MAP and DAP were decreased at 30 min with no change in HR, CVR, SVR, or LV dP/dt. However, in group III, the decreases in MAP and DAP was associated with a decrease in CVR and SVR without a change in LV dP/dt. Increased HR and art NE were observed in this group.

Discussion. Compared to the stable F control dogs, significant systemic and coronary vasodilating effects of N during isoflurane anesthesia were present at the higher level of N (group III). When the blood pressure was reduced by 20%, a compensatory tachycardia occurred that was not associated with an increase in CI, in contrast to the findings of Tosone, et al. Despite hypotensive effects in group II and III and tachycardia in group III, these levels of N were tolerated in this model with presumed normal coronary anatomy since no changes in global myocardial oxygenation were seen. Use of higher levels of N or F in combination, or the presence of ischemic heart disease may result in different effects on myocardial oxygen balance or on the distribution of CSBF.

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Table 1. Control	n	CSBF (ml min^{-1})	CVR (mmHg ml min^{-1})	MVO$_2$ (ml min^{-1})	MLER (%)	NE (art) (pg ml^{-1})
Group I	6	105 ± 14	0.81 ± 0.13	8.0 ± 0.8	26 ± 1	215 ± 65
Group II	5	181 ± 36	0.43 ± 0.10	8.3 ± 1.6	25 ± 5	102 ± 8
Group III	6	161 ± 18	0.50 ± 0.07	11.8 ± 1.4	29 ± 3	143 ± 15
30 min						
Group I	6	100 ± 14	0.82 ± 0.14	8.1 ± 0.9	42 ± 12	146 ± 40
Group II	5	125 ± 23*	0.39 ± 0.07	6.4 ± 1.2	23 ± 3	130 ± 27
Group III	6	241 ± 34	0.22 ± 0.04*	13.4 ± 1.8	18 ± 2	270 ± 57*

Table 2. Control	n	HR (bpm)	MAP (mmHg)	DAP (mmHg)	SVR (dynes·s cm^{-5})	dP/dt (mmHg s^{-1})
Group I	6	134 ± 5	110 ± 6	87 ± 7	2185 ± 321	2538 ± 195
Group II	5	130 ± 3	91 ± 4	74 ± 5	1343 ± 224	2400 ± 346
Group III	6	131 ± 3	97 ± 5	81 ± 5	1766 ± 261	2383 ± 172
30 min						
Group I	6	135 ± 6	96 ± 4	80 ± 4	2238 ± 398	2366 ± 183
Group II	5	132 ± 3	70 ± 3*	52 ± 3*	1063 ± 171	2180 ± 300
Group III	6	147 ± 6*	77 ± 2*	57 ± 1*	1028 ± 120*	2400 ± 276

* = $p < .05$ compared to control.

Title: THE EFFECT OF DIFFERENT ANESTHETICS ON A CONTINUOUS VECURONIUM INFUSION

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Introduction. Vecuronium bromide has a short duration of action and little cumulative effect when given by repeated boluses. Vecuronium administered by continuous infusion for long surgical procedures would thus be a useful technique. In this study, we define the continuous infusion dose requirements for vecuronium during N_2O/enflurane, N_2O/isoflurane, and N_2O/fentanyl anesthesia, and also determine the plasma concentration of vecuronium necessary for 90% depression of control muscle twitch height ($Cp_{ss}90$).

Methods. Seventeen ASA Class I and II patients undergoing elective surgery were studied after giving written, informed consent, as approved by the our Committee on Human Research. Patients were premedicated with diazepam 10 mg p.o. and anesthesia was induced with thiopental 4-8 mg/kg iv. Patients were then randomly assigned to receive N_2O/enflurane (Group I, n=6), N_2O/isoflurane (Group II, n=6), or a N_2O/fentanyl infusion technique (1) (Group III, n=5). A control muscle twitch response was obtained from the thumb via a Grass FT-10 force-displacement transducer, during supramaximal 0.15 ms square-wave ulnar nerve stimulation at 0.15 Hz, delivered via subcutaneous steel-needle electrodes placed at the wrist. After 10 min of stable recording, vecuronium, 0.1 mg/kg iv, was given and endotracheal intubation performed. Following intubation, anesthesia was maintained with nitrous oxide, 60% in oxygen, and depending on the group, enflurane (1.3% end-tidal), isoflurane (1.1% end-tidal), or a fentanyl infusion (0.09 mcg/kg/min). When the muscle twitch response recovered to 10% of control, a vecuronium infusion (200 mcg/ml in normal saline), delivered by a Harvard infusion pump, was begun at 1.0 mcg/kg/min, and adjusted to achieve a 90% depression of twitch height. After reaching a stable infusion rate that maintained 90% twitch depression for one h, blood samples were drawn for determination of $Cp_{ss}90$. The infusion was then discontinued and the neuromuscular block allowed to regress spontaneously. Data obtained included the final infusion rate, the time to establish the final infusion rate, and the length of infusion. $Cp_{ss}90$ values for vecuronium were determined by capillary column gas chromatography using a method developed in this laboratory. Data were compared between groups by analysis of variance and Student-Newman-Keuls test ($P<0.05$).

Results. Table I shows $Cp_{ss}90$ values and final infusion rates for the three groups. Final infusion rates were established between 7 and 129 min after beginning the infusion; duration of infusions ranged from 73 to 340 min. Neuromuscular block began to spontaneously recover in all patients immediately after terminating the vecuronium infusion. The final infusion rates and $Cp_{ss}90$ values in Group III were significantly greater than those in Groups I and II. Groups I and II did not differ from each other.

Discussion. Previous investigators have demonstrated that vecuronium infusion rates necessary to maintain 90% depression of control muscle twitch during N_2O/fentanyl anesthesia vary widely from 0.18 to 2.2 mcg/kg/min (2,3). Similar variability was noted in this study. The coefficients of variation (SD/mean x 100%) for final infusion rates in Groups I, II, and III were 41%, 38%, and 48%, respectively. However, when the SD's are examined in an absolute sense, the N_2O/fentanyl group (SD=0.50) showed more variability than Group I (SD=0.14) and Group II (SD=0.10). The final infusion rate in the N_2O/fentanyl group was 3 times greater than that for either the enflurane or the isoflurane groups. This is in contrast to dose-response studies performed by bolus injection, which demonstrated that N_2O/fentanyl anesthesia required approximately 1.4 times as much vecuronium to achieve the same degree of neuromuscular blockade, when compared to enflurane or isoflurane techniques (4). $Cp_{ss}90$ values suggest that these differences in dose requirements between groups can be explained by pharmacodynamic differences, rather than pharmacokinetic ones. In summary, we have shown that enflurane and isoflurane markedly reduce the amount of vecuronium needed to maintain stable neuromuscular blockade. Because dose requirements are variable, close attention to neuromuscular monitoring is an important part of continuous infusions of vecuronium.

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Table I. (mean ± SD)

Group	Final Infusion Rate (and Range) (mcg/kg/min)	$Cp_{ss}90$ (ng/ml)
I Enflurane (n=6)	0.34 ± 0.14 (0.10 - 0.50)	89.5 ± 18.4
II Isoflurane (n=6)	0.26 ± 0.10 (0.10 - 0.40)	50.4 ± 26.4
III Fentanyl (n=5)	1.04 ± 0.50* (0.50 - 1.75)	156.7 ± 35.7*

* = significant difference from I and II

Title: EFFECT OF ANESTHETIC DURATION ON INHALED ANESTHETIC PHARMACOKINETICS

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Introduction. We measured the pharmacokinetics of inhaled anesthetics after a 30 min anesthetic administration and compared the results with those previously determined for a two hour administration. The comparison defined the effects of the duration of anesthetic administration on the 1) rate of the alveolar washout ; 2) time constants for washin/washout of tissue; 3) number of compartments identified; 4) relative metabolism of the anesthetics; and 5) distribution of the anesthetics to the tissues.

Methods. After obtaining approval by the Committee on Human Research and informed consent, we established anesthesia with nitrous oxide in 7 healthy patients ventilated to maintain normocapnia. A mixture of isoflurane, enflurane, halothane, and methoxyflurane, each at 0.3 MAC, was administered for thirty minutes. Ventilation (VE) and end-tidal, mixed-expired (ME), and inspired (FI) anesthetic concentrations were measured during administration and for 3 to 7 days thereafter. We fit 4 and 5 compartment models to the decay of the alveolar washout of each anesthetic. Uptake and elimination per minute were calculated as VE(FI-ME) and total uptake and total elimination were calculated. Total elimination was divided by total uptake to equal the percent recovered. Because isoflurane is minimally metabolized, we normalized the percent recovered to isoflurane: deficits in normalized recovery were assumed to result from metabolism. To assess the distribution of anesthetic to each compartment of the five compartment models, elimination from a given compartment was estimated as the ratio of the coefficent/exponent divided by the sum of the ratios for all five compartments.

Results. The FA/FAO ratios declined more rapidly (FAO is the alveolar concentration just prior to beginning washout) after the shorter anesthesia, and the halothane ratio fell below the isoflurane ratio 84 min into the washout period (compared to 203 min after the 2 hour administration) (Figure 1). In 25 of 28 comparisons a five compartment model provided a significantly better fit than a four compartment model. We recovered 101.8 ± 1.1% of the isoflurane taken up. Percentages of metabolism for enflurane, halothane, and methoxyflurane were 10.8 ± 1.2%, 41.4 ± 1.4%, and 79.6 ± 1.5%, respectively.

Discussion. More rapidly equilibrating tissues acquired a greater percent of the anesthetic taken up during the shorter administration (Table 1b) and, largely as a result of this, the alveolar washout was more rapid (Figure 1). However, the relative positions of the washout curves, the time constants (Table 1a), and the number of compartments defined were comparable for the two anesthetic durations. The relative rates of metabolism were consistent with those determined in the two hour administration. The totals for both studies suggest that a greater percentage of anesthetic is eliminated by metabolism than previously thought.

The halothane washout curve crossed the isoflurane curve in both studies, indicating that elimination of halothane is more rapid, despite a greater solubility in blood. We attribute this increased elimination to metabolism of halothane. Although the halothane and isoflurane curves cross significantly earlier after the shorter administration ($p<0.02$), the halothane concentrations at the time of crossover are equivalent (0.0046 and 0.0047%). This finding supports our suggestion that metabolism plays a greater role in the total elimination of halothane as the partial pressure approaches the K_m (the partial pressure at which metabolism occurs at half the maximum rate). Because the washout occurs more rapidly after a brief anesthesia, the effect of metabolism is seen earlier in the washout period, suggesting that metabolism plays a greater role in recovery from shorter durations of halothane anesthesia.

Table 1. Comparison of 30-min and 2-hr Anesthetic Administration

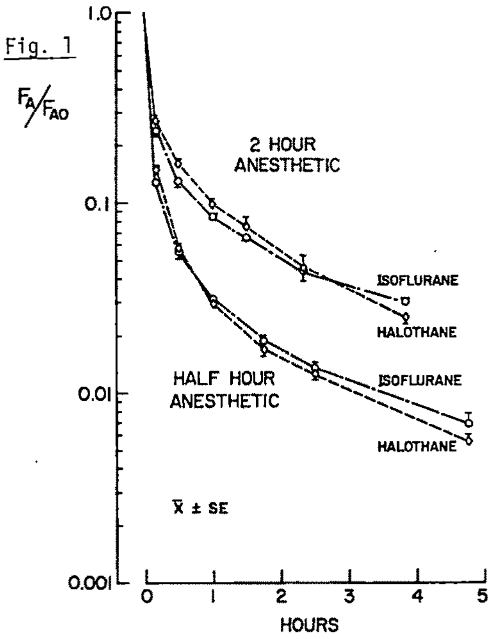
a) Isoflurane Time Constants (min)

	Compartment				
	1	2	3	4	5
30-min	0.3 ± .02	6.1 ± 0.4	56.2 ± 2.8	405 ± 36	2307 ± 398
2-hr	0.2 ± .03	6.7 ± 1.3	77.0 ± 8.4	500 ± 163	3465 ± 176

b) Isoflurane Recovery Assigned to Each Compartment (%)

	Compartment				
	1	2	3	4	5
30-min	1.2 ± 0.1	14.4 ± 1.2	27.2 ± 3.3	30.1 ± 2.7	27.0 ± 5.5
2-hr	0.3 ± 0.1	5.7 ± 1.1	26.6 ± 1.0	33.7 ± 2.5	33.6 ± 3.2

Fig. 1



Title: HEMODYNAMIC CHANGES AND HISTAMINE RELEASE FOLLOWING ADMINISTRATION OF PROTAMINE, VIA A CENTRAL VEIN OR PERIPHERAL OR LEFT ATRIUM: A COMPARATIVE STUDY

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Introduction. Routine administration of protamine following cardiopulmonary bypass is often associated with significant decreases in cardiac output and arterial blood pressure. However, a recent report has shown no hemodynamic changes following administration of protamine. This study was undertaken to compare hemodynamic changes in dogs with good ventricular function following administration of protamine via three different sites: left atrium (group A), right atrium (group B), and peripheral vein (group C).

Methods. Thirty dogs were studied and divided into three groups. Group A had protamine administered via a left atrial (LA) line; group B had the protamine administered via central vein; group C was given via a peripheral vein after previous administration of 4 mg/kg of heparin. The rate of administration of protamine was 1 mg/kg/min in all three groups and the amount given was 4 mg/kg.

Results. Protamine administration through the central venous pressure (CVP) line resulted in significant hemodynamic changes. Mean arterial pressure decreased from 72 ± 7 to 60 ± 4.5 mm Hg ($p < .025$) after the protamine and to 58 ± 5 five minutes later ($p < .025$). Mean arterial pressures were statistically unchanged after administration of protamine through the peripheral vein and left atrium. Cardiac index (CI) increased from 2.8 ± .25 $L/min/m^2$ soon after the protamine to 3.7 ± .3 ($p < .005$) then decreased to 2.7 ± .3 ten minutes later. No significant changes in CI occurred after administration of protamine to the peripheral line or LA line. Systemic vascular resistance (SVR) decreased significantly only after administration of protamine via the CVP and was statistically unchanged when administered via the peripheral and LA Line. Pulmonary vascular resistance was significantly increased only in group B. Histamine levels increased significantly only following administration of protamine through the central line. No significant changes occurred after the administration through the peripheral veins and left atrium. No statistically significant changes occurred in activated clotting time (ACT) between the three groups studied.

Conclusion. Significant hemodynamic changes occurred after protamine administration via the CVP. This is most probably due to massive histamine release due to C3a, C5a anaphylactoxin generation. When protamine was administered via the LA and peripheral veins, the cardiovascular changes were minimal because it bypassed the lungs therefore causing minimal histamine release. The ability of protamine to reverse heparin was the same independent of the site of administration.

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Table: Cardiovascular changes following protamine administration.

		Protamine Infusion		
		Before	After	10 min later
ACT	A	480 ± 10.5	120 ± 7	125 ± 7.5
	B	490 ± 11.0	115 ± 7.5	110 ± 7.0
	C	495 ± 15.0	104 ± 8.5	105 ± 7.5
Histamine**	A	1.5 ± .8	2.75 ± 1	3.1 ± 1.2
	B	1.85 ± .75	8.5 ± .95	8.6 ± 1.2
	C	1.90 ± .85	2.90 ± 1.2	2.85 ± 1.05
HR@	A	95 ± 7	92 ± 8	96 ± 7.5
	B	90 ± 6.5	92 ± 5	93 ± 6
	C	92 ± 6	94 ± 4.5	91 ± 5
BP#	A	70 ± 7	68 ± 6	71 ± 7.5
	B	72 ± 7	60 ± 4.5*	58 ± 5*
	C	75 ± 8.5	70 ± 7	69.5 ± 7.2
PAP#	A	18 ± 1.5	17.5 ± 2	18.5 ± 1.5
	B	16.5 ± 1	10.5 ± .5	10.75 ± .40
	C	17.75 ± 1	17.5 ± 1.5	13 ± 1.20
RAP#	A	7 ± .5	6 ± .4	5 ± .5
	B	8 ± .5	3 ± .1	4 ± .15
	C	7.5 ± .5	7 ± .6	7.5 ± .5
CI+	A	2.7 ± .2	2.8 ± .25	2.75 ± .3
	B	2.8 ± .25	3.70 ± .3	2.70 ± .3
	C	2.75 ± .3	2.8 ± .35	2.9 ± .4
SVR¶	A	25.5 ± 2	22.14 ± 1.9	24 ± 2.2
	B	26 ± 2.5	15.40 ± 1	20 ± 1.25
	C	24.5 ± 2.4	22.5 ± 2.5	21.37 ± 2.15
PVR¶	A	5.7 ± .5	4.70 ± .5	5.2 ± .45
	B	5.9 ± .6	10.05 ± .1	8.07 ± .30
	C	6 ± .55	5.60 ± .3	5.40 ± .4

** ng/ml, @ beats/min, # mm Hg, + $L/min/m^2$, ¶ U · m, Group A - LA, Group B - CVP, Group C - peripheral.

Title: OPIOID AGONIST FOR SPINAL ANALGESIA WITHOUT RISK OF RESPIRATORY DEPRESSION

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Introduction. Spinal or epidural administration of morphine has a delayed life-threatening respiratory depression as a serious side effect. We hypothetized that opioid-induced analgesia and respiratory depression are mediated through different subtypes of opioid receptors and therefore opioid agonists selective for certain subtypes of the receptors may provide spinal analgesia without risk of respiratory depression. The purpose of this study was to find out whether selective kappa opioid agonist, U-50,488H (1) can provide spinal analgesia with somatic mechanical stimulation without the potential risk for respiratory depression.

Methods. Sixty-two male Sprague-Dawley rats (300-350g) with chronically implanted lumbar or cerebroventricular catheters were used for the study. As a nociceptive test, we used motor response to the increasing pressure on the tail (2) provided with an Analygesy-meter (Ugobasile). Pressure was increased at the constant rate of 80 g/sec until the animal made an attempt to escape. The reaction threshold to the pressure was measured every 15 minutes before administration of an agent, and four to six times after it. Respiratory depression was determined with two methods: by measuring $PaCO_2$ in samples of blood obtained from a chronically implanted arterial catheter, and by measuring the respiratory rate through registration of chest movements. The following series of experiments were performed: analgesia series with spinal administration of agents and two respiratory depression series with intracerebroventricular injections. In each series of experiments, there were subseries of experiments with U-50,488H and with a reference agent - morphine sulfate. In the analgesia series U-50,488H was used in doses of 10, 20, and 50 μg and morphine in doses of 1, 2, and 5 μg. In the respiratory depression series, U-50,488H was used in doses of 50, 100, and 300 μg and morphine in doses of 1, 5, and 10 μg. Each animal was given only one dose of an agent.

Results. U-50,488H caused a dose-dependent increase in reaction threshold for noxious mechanical stimulation (Table). Its potency was approximately 1/13 of morphine. Respiratory depression was observed with all studied doses of morphine and it was not present in the rats treated with equipotent doses of U-50,488H (Figure).

Discussion. Absence of respiratory depression with U-50,488H agrees with the viewpoint that opioid-induced respiratory depression is mediated by mu-2 and/or delta receptors (3). Because U-50,488H is a very selective kappa opioid agonist (1), it probably does not interact with any subtypes of opioid receptors that mediate respiratory depression. It was shown (4) that U-50,488H demonstrates an antinociceptive effect against visceral chemical stimulation but not cutaneous thermal stimulation. Our data suggest that U-50,488H has an antinociceptive effect against mechanical somatic stimulation.

In rats, selective kappa opioid agonist, U-50,488H provides epidural analgesia and has no potential for respiratory depression. These data warrant clinical study to prove that kappa opioids may be used for spinal and epidural analgesia without risk of respiratory depression.

Table. Effect of intratheeal U-50,488H and morphine on motor reactions threshold to mechanical noxious stimulation.

Dose (μg)	N	Threshold Δ %, Mean	SEM
		U-50,488H	
10	4	43	5
20	4	60	10
50	4	92	6
		Morphine	
1	4	45	3
2	4	76	23
5	4	96	4

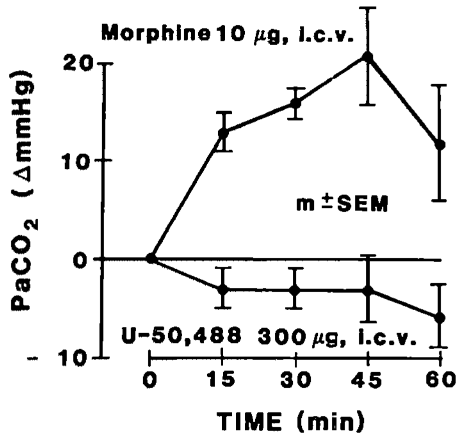

Figure. Effect of intracerebroventricular U-50,488H and morphine on $PaCO_2$.

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Title: NONINVASIVE RESPIRATORY MONITORING OF PATIENTS DURING WEANING FROM MECHANICAL RESPIRATORY SUPPORT

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Introduction. During recovery from aortocoronary bypass surgery patients progress through various stages of ventilatory support from controlled mandatory ventilation (CMV), intermittent mandatory ventilation (IMV), and continuous positive pressure ventilation (CPAP) to extubation. The objective of this study was to compare various noninvasive methods of monitoring respiratory function with routine intermittent arterial blood gas (ABG) analysis. Transcutaneous oxygen and carbon dioxide tensions ($PtcO_2$, $PtcCO_2$) and end-tidal carbon dioxide ($PetCO_2$) were compared to arterial oxygen and carbon dioxide tension (PaO_2, $PaCO_2$). Pulse oximeter arterial oxygen saturation ($pSaO_2$) was compared to arterial oxygen saturation (SaO_2). The study was designed to determine whether these methods could replace ABG analysis in the face of changing intrapulmonary shunt, dead space ventilation, temperature, and skin and finger perfusion during different phases of ventilatory support.

Methods. After institutional approval and informed consent was obtained, twelve adult patients recovering from elective aortocoronary bypass surgery were studied. All patients had received a similar narcotic/relaxant/oxygen anesthetic technique. All patients were ventilated with CMV on a Bourne's Bear 1 volume ventilator, and then weaned through IMV and CPAP to extubation by standard clinical criteria. Noninvasive monitors were placed immediately after admission to the intensive care unit (ICU). After calibration a common sensor heated to 44°C for the Novametrix 818 Transcutaneous O_2/CO_2 monitor was placed on the anterior chest wall. The sensor was recalibrated and its position was changed every 3-6 hours. $PtcO_2$ and $PtcCO_2$ data were included for analysis only after a 30 minute warm-up time following each sensor relocation. The $pSaO_2$ was monitored with the Nellcor N-100 pulse oximeter. A side port sensor for the Puritan-Bennett CO_2 monitor was inserted at the Y of the ventilator circuit for monitoring of $PetCO_2$. Analog signals were continuously recorded from these four monitors on a 4 channel stripchart recorder (HP 7754A). Heart rate and rhythm was monitored with a standard lead II electrocardiogram. Temperatures were measured with probes on a finger, on the anterior chest wall, and in the rectum (YSI Tele-thermometer). Exhaled gases were collected in a 60 L Douglas bag over a three-minute period using a Puritan-Bennett gas collection manifold. Mean arterial pressures and blood samples were obtained from a radial artery catheter. Exhaled air was analysed for mixed expired CO_2 (P_ECO_2); arterial blood samples for SaO_2, PaO_2 and $PaCO_2$ (Il 282 co-oximeter, Corning 168 blood gas machine). Dead space to tidal volume ratio (V_D/V_t) was derived by the Bohr equation ($PaCO_2$-P_ECO_2/$PaCO_2$). Data were collected every hour from the time of patient arrival to the ICU until two hours post-extubation in each patient.

Results. A total of 254 data sets were recorded in 12 patients (age 46-70). The range of measured SaO_2 was small (85-100%). The $pSaO_2$ was significantly different from SaO_2 ($t=8.8$, $p < .0001$) but this difference was small (1.2±.4, mean±SE). However, there were 5 "desaturation" episodes lasting 1-3 minutes where $pSaO_2$ was <90% (81±3%, mean±SE) and SaO_2 was >90% (96±1%, mean±SE). In each event patient agitation and vigorous movement of the extremity with the sensor occurred. Finger temperature (21.5-37.7°C) did not affect the accuracy of $pSaO_2$. However, on 10 occasions in 2 patients at 24.3-26.2°C, no signal could initially be detected. There was no relationship between the accuracy of $PtcO_2$, $PtcCO_2$ and skin temperature (27.9-38.2°C). V_D/V_t varied during the study period and decreased significantly during CPAP (CMV .44±.02, IMV .39±.02, CPAP .32±.03, extubated .40±.04, mean±SE). Increasing values of V_D/V_t correlated with larger $PaCO_2$-$PetCO_2$ differences ($y=33.8x-13.5$, $r=.67$, $n=221$, $p<.0001$). Table 1 summarizes linear regression analysis (r=correlation coefficient, n=sample size) for all data from $PtcO_2$, $PtcCO_2$ and $PetCO_2$. $P < 0.05$ for all correlation coefficients.

Table 1

		Total	CMV	IMV	CPAP	Extubated
$PtcO_2$	r	.62	.62	.76	.50	.60
vs PaO_2	n	204	118	38	21	27
$PtcCO_2$	r	.67	.70	.66	.55	.70
vs $PaCO_2$	n	205	119	38	21	27
$PetCO_2$	r	.72	.80	.46	.51	.70
vs $PaCO_2$	n	245	148	41	26	30

In order to determine trending capability, pairs of data that met one of the following criteria were subjected to regression analysis (Table 2): >10% change in PaO_2, $PaCO_2$ vs. $PtcO_2$, $PtcCO_2$; or >5 mmHg change in $PaCO_2$ vs. $PetCO_2$. Data include the incidence of trending in opposite directions to ΔPaO_2 or $\Delta PaCO_2$ (false positive) as well as the incidence of indicating no change when PaO_2 or $PaCO_2$ had actually changed (false negative).

Table 2

	r	n	False Positive	False Negative
$\Delta PtcO_2$ vs. ΔPaO_2	.65	121	27%	0%
$\Delta PtcCO_2$ vs $\Delta PaCO_2$	.70	89	18%	6%
$\Delta PetCO_2$ vs $\Delta PaCO_2$	.77	84	14%	4%

Discussion. We conclude that all four noninvasive monitors could augment clinical observations and provide more objective indications for ABG analysis. The trending capability of the noninvasive monitors was good but in three ($PtcO_2$, $PtcCO_2$, $PetCO_2$) there was an unacceptable incidence of false positive and false negative information. At this time therefore, none are accurate enough to obviate completely the need for intermittent ABG analysis after elective aortocoronary bypass surgery.

Title: **CONTINUOUS INFUSION EPIDURAL ANALGESIA WITH LIDOCAINE: INFLUENCE ON THE SECOND STAGE OF LABOR**

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Introduction. There is controversy regarding the influence of epidural analgesia on the second stage of labor. Phillips and Thomas[1] reported no increase in duration of the second stage, and a decrease in the incidence of instrumental delivery, in primigravid patients whose epidural anesthetic was "topped up" with bupivacaine during the second stage, as compared with patients given no additional "top-ups." The purpose of this investigation was not only to assess the efficacy of continuous infusion epidural lidocaine during the first stage of labor, but also to evaluate its analgesic efficacy and potential influence during the second stage of labor.

Methods. The protocol was approved by the local institutional review board for human research. Written informed consent was obtained from 33 uncomplicated primigravid patients with a term singleton fetus of vertex presentation. An epidural catheter was placed via the L2-3 or L3-4 interspace when the cervix was $\geq$ 4 cm and $\leq$ 7 cm dilated. Each patient received 3 ml of 1.5% lidocaine with 1:200,000 epinephrine, followed by 4-6 ml of 1.0% lidocaine. Each patient then received a continuous infusion of 0.75% lidocaine, via a Harvard pump, at an initial rate of 12-14 ml/hr; the rate was adjusted upward or downward to maintain a cephalad dermatomal level of T10. Motor block was assessed according to the method of Bromage[2] (none, partial, almost complete, complete). When the cervix was $\geq$ 8-9 cm dilated, a 60 ml syringe of unidentified study solution was substituted for the syringe containing 0.75% lidocaine. The infusion was then continued, with no change in rate, until after delivery. Each syringe of study solution was prepared by the hospital pharmacy according to previous randomization, and was administered in a double-blind manner. The study solution for Group L patients was 0.75% lidocaine; Group S patients received normal saline. Each patient was encouraged to assume the 45° upright position and was allowed to push when cervical dilatation was complete. Each patient was asked to assess the quality of her analgesia (excellent, good, fair, poor, very poor) during the first and second stages of labor. The method of delivery was chosen according to obstetric indications only; elective forceps deliveries were not performed. Pudendal block and/or perineal infiltration with 1.0% lidocaine were performed as indicated. Neonatal assessment was by Apgar scores and cord blood gases. Statistical analysis was by Wilcoxon analysis and Fisher's exact test as indicated. $P < .05$ was considered statistically significant.

Results. Six patients underwent cesarean delivery prior to start of the study solution and were excluded. Among the remaining 27 patients, there were 14 patients in Group L and 13 patients in Group S. The two groups were similar with regard to age, race, socioeconomic status, weight, gestational age, and cervical dilatation at the start of epidural analgesia (Group L = 5.2 ± 1.1 cm, Group S = 5.3 ± 1.4 cm.). Motor block in all patients was either none or partial. The table includes results regarding length of labor, method of delivery, and newborn status.

	Group L N = 14	Group S N = 13	P Value
Duration of first stage, in minutes ($\geq$ 4 to 10 cm)*	411 ± 264	400 ± 297	NS
Duration of second stage, in minutes*	58 ± 73	65 ± 45	NS
Method of Delivery			
Spontaneous	13	8	NS
Low Forceps	0	3	
Mid Forceps	1	1	
Cesarean	0	1	
Infant Weight*	3220 ± 586	3188 ± 497	NS
1 minute Apgar $\geq$ 7	14(100%)	8(62%)	.02
5 minute Apgar $\geq$ 7	14(100%)	12(92%)	NS
Umbilical vein pH*	7.31 ± .05	7.29 ± .09	NS
Umbilical artery pH*	7.24 ± .06	7.23 ± .08	NS

*Mean ± S.D.

One of 14 (7%) patients in Group L, versus 5 of 13 (39%) patients in Group S, had operative delivery (P = .08). Eleven of 14 (79%) patients in Group L, and 12 of 13 (92%) patients in Group S, rated their first stage analgesia as excellent or good (P = NS). Twelve of 14 (86%) patients in Group L rated their second stage analgesia as excellent, good, or fair, versus 8 of 13 (62%) patients in Group S (P = NS).

Discussion. Continuous infusion epidural lidocaine provided clinically acceptable analgesia during the first stage of labor. Continuation of the epidural lidocaine infusion during the second stage was not associated with a prolongation of the second stage or an increase in the incidence of operative deliveries, although Group L patients had only a modest improvement in second stage analgesia. The higher frequency of low one minute Apgar scores in Group S is not entirely explicable and warrants further investigation.

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Title: CSF MORPHINE CONCENTRATIONS AFTER ADMINISTRATION OF SUSTAINED RELEASE MORPHINE PER OS AND MORPHINE-HCL I.M. IN DOGS

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Introduction. Recently the incidence of respiratory depression following oral administration of sustained release morphine (MST) has been the subject of much discussion (1,2,3). In light of the relationship between cisternal cerebellomedullary CSF morphine concentrations and respiratory depression (4), the aim of the present investigation was to examine cisternal cerebellomedullary CSF concentrations of morphine in dogs after oral administration of MST and after a bolus intramuscular injection of morphine-HCl.

Methods. Ten dogs, weighing 25 - 32 kg, had catheters (d=1,3mm) inserted into the cerebellomedullary cistern and sewed to the skin under pentobarbital anaesthesia. After regenerating they received randomly either 30 mg (n=8), 60 mg (n=6) or 90 mg (n=7) MST per os or 20 mg morphine-HCl i.m. (n=7). Cisternal cerebellomedullary CSF samples were taken at varying intervals to determine morphine immunoreactivity by radioimmunoassay (Diagnostic Products Corporation, Los Angeles).

Results. Dose dependent plateau concentrations of 6 ng/ml (30 mg MST), 14 ng/ml (60 mg MST) and 40 ng/ml (90 mg MST) were reached after 4, 2.5 and 4.5 hours and remained at a level of 6 ± 1.8 ng/ml, 13 ± 1.7 ng/ml and 12 ± 3 ng/ml, 12 hours after oral administration of MST and at a level of 1 ± 0.4 ng/ml, 5 ± 1.6 ng/ml and 9 ± 1.6 ng/ml after 24 hours, respectively (fig. 1). In contrast, one hour after intramuscular administration of 20 mg morphine-HCl a peak morphine concentration of 102 ± 12 ng/ml was reached, which subsequently declined to 3 ± 0.4 ng/ml after 12 hours and 1 ± 0.3 ng/ml after 24 hours.

Discussion. Our results indicate that even when 90 mg MST are administered orally, morphine concentrations near the respiratory centre do not even reach half the level found after i.m. administration of 20 mg morphine-HCl. Because of the long lasting plateaus of morphine concentrations in the cerebellomedullary cistern under oral MST, administration at short intervals will, however, result in an accumulation of morphine near the respiratory centre, thus increasing the risk of respiratory depression. A decline in excitatory input at the respiratory centre, e.g. by supplementary administration of centrally depressing drugs (3), by chordotomy (1) or by decreasing postoperative pain (3) reqires then special attention.

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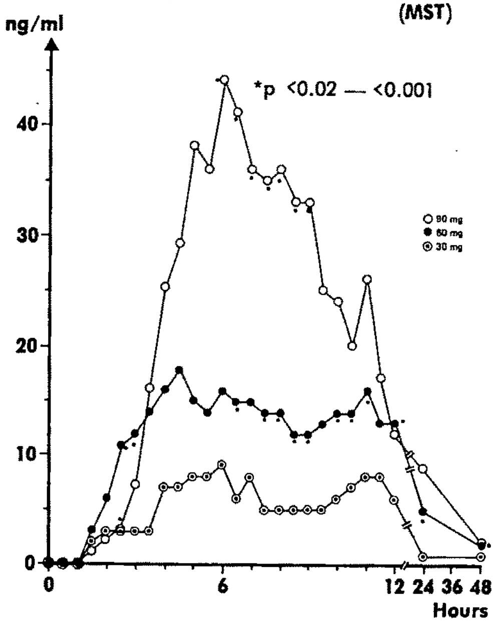
fig. 1

Cisternal cerebellomedullary CSF morphine concentrations after administration of **30, 60 and 90 mg sustained-release-morphine (MST)**



TITLE: TERMINATION OF ATRIAL FLUTTER IN POSTOPERATIVE CARDIAC SURGICAL PATIENTS BY TRANSESOPHAGEAL PACING

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INTRODUCTION

Transesophageal atrial pacing has been used to terminate atrial flutter induced by electrical stimulation during electrophysiologic studies.[1] This report summarizes our experience of applying this technique to terminate atrial flutter developed spontaneously in patients following cardiac surgery.

Methods

Induction and termination of supraventricular tachyarrhythmias by transesophageal atrial pacing is a recognized technique in the cardiac electrophysiology unit of our institution. This procedure was carried out in five consecutive cardiac surgical patients referred to us with the diagnosis of atrial flutter. All patients gave informed consent and the procedure was performed at the bedside in an acute or subacute care area. The esophageal lead used for recording and pacing had a bipolar electrode with an interpolar distance of 2.9 cm (Medtronic 6992), and the pacing unit was a variable-rate constant-pulse generator with pulse strength adjustable between 0 & 37.5 mA and pulse duration between 0 & 9.9 ms. With the patient lying supine and monitored by sphygmomanometry, surface ECG, and transesophageal electrogram, the esophageal electrode was introduced via the nose to near the site of minimum stimulation threshold: either to the site where the amplitude of the atrial component of the esophageal electrogram was maximum or to a depth equal to the distance between the patient's earlobe and the distal end of the sternum. The pulse duration of the generator was set at 9.9 ms, the pulse amplitude at 15 - 20 mA. Pacing commenced at a pacing cycle length that was 20 ms shorter than the patient's atrial cycle length, and a burst lasting 5 - 10 seconds was delivered. If this proved unsuccessful the pacing cycle length was decreased by 20 ms increments and the burst was repeated until atrial flutter was terminated. The procedure was considered unsuccessful if the termination of atrial flutter was not observed when the pacing cycle length has reached 80 - 100 ms.

Results

All patients were male between the age of 48 and 69 years old: four had coronary artery bypass graft and one had aortic valve replacement. Four patients developed atrial flutter within the first postoperative week and one patient, in the third postoperative week. All had received therapeutic doses of one or more of the following drugs in the last 24 hours for attempted pharmacologic cardioversion or control of ventricular rate: digoxin, quinidine, and propranolol. Their atrial cycle length during atrial flutter varied between 200 & 220 ms. Bursts of transesophageal atrial pacing were successful in terminating atrial flutter in all five patients: immediate conversion to sinus rhythm in three, to atrial fibrillation for two minutes followed by sinus rhythm in the fourth, and to atrial fibrillation in the fifth. The last patient stayed in atrial fibrillation for one hour and then reverted to atrial flutter followed by sinus rhythm shortly after receiving quinidine intravenously. The pacing cycle length resulting in the termination of atrial flutter varied between 140 & 160 ms. All patients felt a fluttering or burning sensation in the precordium during pacing and none had described the procedure as unpleasant. No post-conversion ventricular arrhythmias were observed. Of the two patients who went into atrial fibrillation, the ventricular rate when in atrial fibrillation was slower than that when in atrial flutter (75 & 101 bpm versus 110 & 136 bpm).

Discussion

We have demonstrated that transesophageal atrial pacing is successful in terminating spontaneous atrial flutter in postoperative cardiac surgical patients. Conversion to sinus rhythm immediately or following a short period of atrial fibrillation after the last pacing impulse is usual. Occassionally a more prolonged period of atrial fibrillation is induced, but the fall in ventricular rate during atrial fibrillation is accompanied by improvements in circulatory dynamics. This technique is safer and more convenient than other electrical means of terminating atrial flutter. Unlike DC countershock it does not require the administration of a general anesthetic and does not seem to cause post-conversion ventricular arrhythmias, even in digitalized patients. Unlike transvenous atrial pacing, it is not invasive and does not require fluoroscopic equipment. The transesophageal lead may be left in place safely and the procedure repeated when necessary.

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Title: BIS-TRIMETHAPHAN NITROPRUSSIDE (TNP): A NEW MORE POTENT "NITROPRUSSIDE"

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Introduction: Bis-trimethaphan nitroprusside (TNP) is a new 1:2 molar salt of the nitroprusside (NP) and the trimethaphan (TM) ions. We compared its hemodynamic (including intracranial pressure measurements) effects and dose-response curves with those of sodium nitroprusside (SNP) alone, trimethaphan camsylate (TMC) alone, and a 1 + 10 weight to weight mixture of both drugs. We also determined whether significant dose reductions of SNP and TMC reported with the use of the 1 + 10 mixture of both drugs[1,2] were due to synergism or additivity.

Methods: Studies were conducted in anesthetized cats in a randomized, comparative multi-crossover design. TNP was prepared by a new method (patent for TNP is pending) and TMC and SNP solutions including 1 + 10 mixture were prepared from commercially available preparations. All test compounds were freshly prepared as 0.09% solutions (9 mg/100 ml) in normal saline. The solutions were randomly infused into five male cats, (weight 3.6 ± 0.15 kg) that were ventilating spontaneously through tracheotomies under nembutal (45 mg/kg, I.P.) anesthesia. Each cat received 5 or 6 separate infusions. Adequate time was allowed between drug infusions for return of mean arterial pressure (MAP) to baseline values (30 min for TNP and SNP, 60 min for SNP and TMC mixture, and 90 min for TMC). The dosage was increased every five min in this order 1, 2, 4, 10 and 40 µg/kg min until each level of hypotension had stabilized, and the lowest level of hypotension was held constant for 15 min. The infusion was then abruptly stopped to provoke rebound. Recovery times were recorded. The following hemodynamic variables were obtained: arterial blood pressure (Miller catheter-tip pressure transducer in the aorta via a femoral artery), heart rate (cardiotachometer), and intracranial pressure (ICP; Statham pressure transducer P 23BB), from the left lateral ventricle.

Results: These are summarized as follows:
1. Plots of log dose-response curves show that (a) TNP (contains only 22.6% NP ion) is as potent as SNP in reducing MAP by 20 mm Hg and is increasingly more potent than SNP at deeper levels of hypotension; (b) the dose of the 1 + 10 mixture required to decrease MAP by 35 mm Hg is three times that of SNP and about one-third that of TMC;
2. On a molar basis (log scale), TNP is 3.5- to 12-fold more potent than SNP and is much more potent than TMC;
3. After abrupt discontinuation, the effects of SNP and TNP rapidly subside with half-lives of about 5 min, whereas the effect of TMC slowly subsides with a half-life of 21 min. Rebound hypertension occurred only with SNP;
4. When MAP is decreased by less than 25 mm Hg, ICP does not change with any of the agents. With greater reductions in MAP, SNP and TMC increase ICP. TNP increases ICP only when MAP decreases by 60 mm Hg;
5. Additivity and synergism (determined by isoboles) studies show that the 1 + 10 mixture is additive at reductions of MAP by 20 mm Hg and synergistic (maximum 200%) when MAP is reduced by 35 mm Hg. The synergism then decreases with increasing hypotension. TNP exhibits a steadily increasing synergism which begins when MAP decreases by 20 mm Hg and increases to about 20-fold at maximum reductions of MAP (80 mm Hg).

Discussion: Vasodilation elicits reflex activation of the sympathoadrenal system. In TNP, the TM ion, by virtue of its ganglionic blocking effect, inhibits reversibly autonomic (reflex) ganglionic transmission. In vitro studies, show that ganglionic blockade by TMC occurs at very low concentrations. In humans, TMC, unlike SNP, does not increase renin and angiotensin II levels[3], and causes small elevations in plasma catecholamines. Thus the efficacy of TNP is the sum of the ganglionic blocking action of TMC and direct vasodilation of the NP ion. This short-lived ganglionic blockade by the TM ion is the pharmacological prerequisite for achieving the full pharmacological potential of the NP ion which would otherwise be increasingly antagonized by the rising levels of vasopressor hormones. Thus TNP may be characterized as a more potent nitroprusside rather than a simple combination of the two hypotensive drugs. This theory may also explain the comparatively small synergistic effect seen with the 1 + 10 mixture of SNP and TMC which rapidly decreases with increasing hypotension, whereas the synergism in TNP steadily increases with increasing hypotension. Currently, studies with TNP are being conducted in humans.

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Title: MONITORING OF MIXED VENOUS OXYGEN SATURATION AS AN INDICATOR OF OXYGENATION DURING THORACIC SURGERY

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Introduction Mixed venous oxygen saturation (SvO_2) is an accepted indicator of cardiac output (CO) and tissue perfusion (1). A decrease in SvO_2 implies a decrease in oxygen delivery or an increase in oxygen consumption. The Fick formula describes the relationship between CO, oxygen consumption, and arteriovenous oxygen content difference, and shows that CO, SvO_2, and SaO_2 are closely related. The SvO_2 is directly proportional to CO when SaO_2, hemoglobin, and oxygen consumption remain constant. When arterial oxygenation (PaO_2) is compromised because of V/Q mismatch, as occurs during one lung anesthesia (OLA) for thoracic surgery, the existing balance between CO, SvO_2, and PaO_2 may be disturbed. This will result in a decrease in oxygen delivery to the periphery and tissue hypoxia. The purpose of this study was to determine whether the continuous monitoring of SvO_2 provides adequate indication of changes in PaO_2 and CO during OLA.

Methods Twenty-six adults, ASA Physical Status I or II, scheduled for pulmonary resection in the lateral position, gave their informed consent to participate in this institutionally approved study. Monitoring was established with a radial arterial catheter, and an Oximetrix Opticath® PA Catheter (Oximetrix, Mountain View, CA), which has the capacity for continuously monitoring SvO_2. Anesthesia was induced with thiamylal sodium 3.5 mg/kg IV. Endobronchial intubation with a Robertshaw double lumen tube was facilitated by succinylcholine 1 mg/kg. Anesthesia and relaxation were maintained with N_2O/O_2 (50/50%), isoflurane 1.0-1.5% (inspired concentration) and pancuronium. Patients were ventilated with a tidal volume of 10 ml/kg and at a rate to maintain $PaCO_2$ within the normal range. SvO_2 was monitored continuously. Hemodynamic measurements and arterial blood gas determinations were obtained 15 minutes following any change in ventilatory mode (two lungs, one lung, PEEP, CPAP) and once stabilization had occurred. PaO_2 was determined from blood gas analysis and compared with SvO_2 measurements obtained via the PA catheter. Temperature and hemoglobin were kept within the normal range. A reduction in PaO_2 compared to the preceding sample, accompanied by a reduction in SvO_2 was defined as a true positive (TP). A simultaneous increase in both was termed a true negative (TN). A decrease in PaO_2 followed by an increase in SvO_2 was termed a false negative (FN), while an increase in PaO_2 associated with a decrease in SvO_2 was a false positive (FP). Specificity (TN/TN+FP), sensitivity (TP/TP+FN) and predictability (TP/TP+FP) of SvO_2 used to detect a reduction in PaO_2 were determined. Similar measures of the relationship between SvO_2 and CO were also determined.

Results PaO_2, SvO_2 and CO were measured simultaneously in 125 situations. Of these, 83 showed changes in SvO_2 greater than 5%, and 42 a greater than 10% change, as compared with the preceding value. The specificities, sensitivities, and predictabilities of using changes in SvO_2 to detect changes in PaO_2 and CO are shown in the Table.

Discussion The Fick formula shows that SvO_2 is related to SaO_2 and hence PaO_2, provided CO and oxygen consumption remain constant. At PaO_2's greater than 100 mmHg, SaO_2 is always 100%, therefore changes in PaO_2 will not be reflected by changes in SvO_2. During OLA with FIO_2 0.5, PaO_2 is usually less than 100 mmHg. The resulting decrease in SaO_2 will be reflected in SvO_2. We have shown that SvO_2 is a sensitive monitor of decreases in PaO_2 during OLA. A 10% decrease in SvO_2 was sensitive to 89% of decreases in PaO_2, while a 5% decrease in SvO_2 had a sensitivity of 75%. Changes in SvO_2 were poor predictors of changes in CO. This is because SvO_2 and CO have opposite trends when PaO_2 is compromised. A decrease in PaO_2 is offset by an increase in CO in an attempt to maintain oxygen delivery. Decreases in SvO_2 are therefore rather insensitive (38%) to decreases in CO during OLA. Monitoring of SvO_2 during OLA is no substitute for periodic blood gas sampling. However, a 10% decrease in SvO_2 should alert the anesthesiologist to a potential decrease in PaO_2 or to inadequacy of some other component of the oxygen delivery system.

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TABLE

Detection of Changes in:

	PaO_2			CO
Changes in SvO_2	Overall	>5%	>10%	Overall
Observations	125	83	42	125
Specificity (%)	81	85	96	58
Sensitivity (%)	84	75	89	38
Predictability(%)	75	80	94	47

Title: THE EFFECT OF EARLY EXTUBATION ON SHUNT AFTER CORONARY ARTERY BYPASS

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Introduction. Studies examining early extubation after coronary artery bypass have been hampered by a lack of control over anesthetic technique.[1,2] This study examines some postoperative results of early extubation compared to late extubation when patients receive the same anesthetic technique.

Methods. Twenty-four patients scheduled for elective, coronary artery surgery, having normal ventricular function, normal resting hemodynamics, and no history of a myocardial infarction within three months were studied after obtaining institutionally approved informed consent. Patients were assigned to either the early or late extubation group in a double blind fashion prior to coming to the operating room. All patients received the following anesthetic regimen. Pre-medication consisted of morphine (0.1 mg/kg IM) and scopolamine (0.4 mg IM) two hrs prior to the induction of anesthesia. Anesthesia was induced with fentanyl (250-500 µg IV) and mask halothane anesthesia in oxygen at a F_IO_2 of 1.0. Muscle relaxation was achieved with dimethyl-tubocurarine (0.4 mg/kg IV). When a sufficient depth of anesthesia had been obtained, as determined by graded response technique, the trachea was intubated and respirations were controlled. Anesthesia was maintained with halothane in oxygen at a F_IO_2 of 1.0. Additionally, morphine (0.2-0.3 mg/kg IV) was administered following cardiopulmonary bypass. At the end of the surgical procedure, reversal of muscle relaxation was achieved utilizing neostigmine (0.06 mg/kg IV) and atropine (0.02 mg/kg IV) and documented by a train-of-four monitor. Intraoperative data recorded included cross-clamp time, cardiopulmonary bypass time, and number of vein bypass grafts.

On arrival in the intensive care unit, all patients had respirations controlled by a volume ventilator with the following parameters: F_IO_2 - 100%, TV - 10-15 ml/kg, RR 8-12 (adjusted to a PCO_2 of 38-42), and a PEEP of 5 cm H_2O. Patients randomized to early extubation were extubated within 6 hrs of arrival in the ICU. Late extubation (control) patients were extubated the morning after surgery. Criteria for extubation included: a responsive patient, normothermia, TV $\geq$ 5 ml/kg, respiratory rate $\leq$ 30 breaths/min, adequate muscle strength, negative inspiratory force of $\geq$ 25 cm H_2O, $F_IO_2 < 0.5$ with $PaO_2 > 70$ mmHg, PEEP $\leq$ 5 cm H_2O, absence of bleeding, and hemodyanamic stability.

Hemodynamic data, arterial and mixed venous blood gases, and hemoglobin concentration were determined on ICU admission, every two hrs for 6 hrs, then every four hrs for 30 hrs. Duration of inotropic and/or vasodilator therapy, amount of morphine, diuretic requirement, amount of postoperative bank blood transfused, time of intubation, and total ICU stay time were recorded for all patients.

Results. Twenty-four patients were studied, 12 control and 12 early extubation. Group comparisons are shown in Table 1. There was no difference between groups in age, weight, height, cross-clamp time, pump time, or number of grafts. The control group was intubated for 16.2 ± 0.9 hrs compared to 5.4 ± 0.1 hrs for the early extubation group ($p < 0.05$). Duration of nipride therapy was not significantly different between groups (13.6 ± 3.2 hrs for control, 14.8 ± 4.2 hrs early ext.); however, amount of morphine required during the ICU stay was significantly different (25.0 ± 4.0 mg IV for control vs. 9.5 ± 2.4 mg IV for early ext., $p < 0.05$). There was no significant difference between groups in amount of lasix or amount of blood given in the ICU. ICU time was not significantly different between groups. The calculated shunt (Qs/Qt) did not differ significantly between groups over the first 30 hrs after ICU admission; however, the control group demonstrated an increased shunt at 26 hrs compared to at 2 and 6 hrs ($p < 0.05$, see Table 2).

Discussion. Foster, et al.[1] reported an unrandomized comparison of 27 control vs. 36 early extuba- tion patients, and showed no significant differences except for number of blood gases drawn. Rankin, et al.[2] have reported improvement in LV diastolic fill- ing associated with early extubation. In our study, the increased shunt in the control group that occurred at 26 hrs may well be atributed to a transitory increase in shunt after delayed extubation in this group. Those patients extubated early showed only a gradual descrease in shunt. We conclude that early extubation after coronary artery bypass in selected patients is safe and is efficacious for (1) decreased ventilator time, (2) gradual decrease in shunt, and (3) decreased requirement for pain medication.

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TABLE 1: GROUP COMPARISONS (mean ± SEM)

	Control	Early Extubation
Age (yrs)	56 ± 3	58 ± 1
Weight (kg)	77 ± 2	83 ± 5
Height (cm)	174 ± 3	171 ± 4
X-clamp (min)	44 ± 4	38 ± 4
Pump (min)	74 ± 5	66 ± 6
No. Grafts	3.6 ± 0.3	3.6 ± 0.3
Intubation (hrs)	16.2 ± 0.9	5.4 ± 0.1*
ICU (hrs)	49 ± 4	42 ± 0.8

* $p < 0.01$ between groups

TABLE 2: Qs/Qt (mean ± SEM)

	Control	Early Extubation
ICU Adm	0.23 ± 0.02	0.23 ± 0.02
2 hrs	0.18 ± 0.01	0.23 ± 0.02
4	0.19 ± 0.02	0.20 ± 0.01
6	0.18 ± 0.01	0.23 ± 0.03
10	0.19 ± 0.01	0.22 ± 0.02
14	0.19 ± 0.01	0.23 ± 0.02
18	0.22 ± 0.01	0.20 ± 0.01
22	0.23 ± 0.03	0.20 ± 0.04
26	0.25 ± 0.03*	0.18 ± 0.04
30	0.20 ± 0.06	0.15 ± 0.03

* $p < 0.05$ from 2 hrs and 6 hrs

Title: EMG RESPONSE TO AUDITORY STIMULI UNDER ISOFLURANE ANESTHESIA

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Introduction. The amplitude of spontaneous frontalis muscle EMG is markedly depressed during surgical anesthesia, even in the absence of neuromuscular blocking agents. Sudden increases observed intraoperatively have been attributed to enhanced patient responsiveness.[1] In fact, frontalis EMG amplitude has been used to assess the adequacy of anesthesia.[2] However, numerous psychophysiological studies have shown that frontalis EMG activity in resting conscious subjects increases during acoustic or cognitive processing.[3] Therefore, we examined the EMG response to the presentation of neutral acoustic stimuli during deep surgical anesthesia.

Methods. Approval was obtained from the Veterans Administration Human Studies Committee. Fifteen ASA I-III adult male subjects were studied with informed consent. Prior to induction of anesthesia a hearing test was performed using earphones and tape recorded words. The standardized anesthetic protocol consisted of glycopyrrolate 0.2 mg IV and diazepam 0.07 mg/kg IV followed 20 min later by a defasiculating 3 mg dose of d-tubocurarine, induction with thiopental 6 mg/kg IV and intubation with succinylcholine 2 mg/kg IV. Anesthesia was maintained with 50:50 N_2O/O_2 and isoflurane. End-tidal concentration of this latter agent was continuously monitored with an infrared analyzer. Approximately 20 min after induction, tape recorded acoustic stimuli (neutral words or sounds) were presented repetitively via earphones for 15 min. The ears were then occluded for the remainder of the surgery. Using adhesive skin electrodes placed over the frontalis muscle and mastoid process, successive 10 sec samples of the mean integrated EMG amplitude (70-300 Hz bandwidth) were digitally recorded. The amplitude of the median 10 sec EMG epoch during acoustic stimulation was compared with the median value obtained in the subsequent 15 min "quiet" period. A paired Student's t test (two-tailed) was used for comparison.

Results. During the 30 min evaluation, end-tidal isoflurane concentration remained relatively constant at 1.1 ± 0.4% ($\bar{X}$ ± SD). The adequacy of anesthesia was evidenced by the absence of marked changes in mean arterial blood pressure, heart rate or end-tidal PCO_2. In all cases, EMG amplitude decreased to near the noise level of the monitoring device during induction. Elevations from this depressed baseline occurred only during acoustic stimulation (horizontal bar in Fig. 1) or from artifactual contamination by movement or electrical interference. Surgical stimulation did not result in enhanced EMG activity in these deeply anesthetized patients. Group mean EMG amplitude during acoustic stimulation was 2.5 ± 0.9 μV compared with 1.6 ± 0.6 μV following stimulation ($P<.01$). No subject had conscious recall of any intraoperative event.

Discussion. This study demonstrates that moderate increases in EMG activity are associated with presentation of acoustic stimuli and are not necessarily indicative of a stress response to surgical manipulation. These results thus provide objective evidence that central processing of acoustic stimuli is not totally suppressd during surgical anesthesia. Although changes in the activity of the spontaneous frontalis EMG may offer useful information during anesthesia, accurate interpretation will require additional study.

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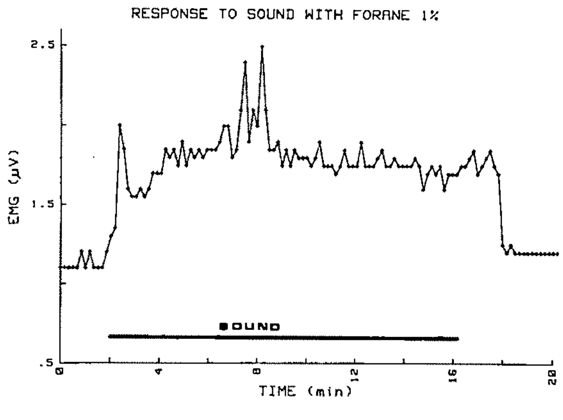

Title: CHEMOREFLEX HYPOCAPNIA CAUSES NON-UNIFORM ANTAGONISM OF HYPOXIC VASODILATION IN CANINE BRAIN

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Introduction. It is well established that locally-mediated vasodilation is a compensatory mechanism tending to maintain oxygenation of brain tissue during arterial hypoxia.[1] Previous studies have demonstrated that, when hypoxia occurs during spontaneous breathing, this hypoxic vasodilation is antagonized by the vasoconstrictor effects of arterial hypocapnia which results from chemoreceptor-mediated hyperventilation.[2] Since these studies utilized blood flow techniques which measured only total cerebral blood flow, it was not evaluated whether regional variation exists in the hypoxia-hypocapnia interaction. The objective of the present study was to evaluate, using the radioactive microsphere technique, regional variation in the ability of hypocapnia, secondary to chemoreceptor-mediated hyperventilation, to counteract hypoxic vasodilation in the brain.

Methods. Studies were conducted in 20 chloralose-anesthetized, mongrel dogs. Animals were intubated and catheters were inserted into 1) the thoracic aorta (via the right brachial artery) for measurement of mean aortic pressure (AOP), 2) the vena cava (via the left femoral vein) for measurement of mean central venous pressure (CVP), and 3) the left ventricle (via the left femoral artery and aorta) for systemic injections of radioactive microspheres. Measurements of regional cerebral blood flow (CBF) were obtained in the cerebral cortex, cerebellum, pons, medulla, and cervical spinal cord with 15μ microspheres. Regional cerebral vascular conductance (CVC) was computed from the equation, CVC = CBF/(AOP-CVP). Measurements of CVC were obtained during the control (normoxic) period and after 4-5 min of inspiration of 5 % O_2 in N_2, at a time when monitored hemodynamic parameters were in a steady state. The dogs were divided randomly into three groups. Dogs of Group I (n=7) were artificially ventilated by a Harvard respirator after undergoing bilateral thoracotomy and muscle paralysis with succinylcholine (1 mg/kg i.v. with supplementation) to prevent chemoreceptor-mediated hyperventilation during arterial hypoxia. Dogs of Groups II (n=6) and III (n=7) breathed spontaneously, so that hyperventilation could occur during hypoxia. In Group II, arterial PCO_2 was permitted to fall during hypoxia, while in Group III it was maintained at control levels by addition of 5 % CO_2 to the inspired hypoxic gas. Statistical analyses were performed using the Student's t test and analysis of variance and Student-Newman-Keuls procedures. $P < 0.05$ was considered significant.

Results. Under control conditions dogs of Groups I, II, III had similar arterial blood gases and pH, which were in the physiological range. In Group I, hypoxia was associated with pronounced reduction in arterial PO_2 (15.4 ± 2.2 mmHg) and with stable arterial PCO_2 and pH. These blood gas responses were accompanied by significant increases in CVC (Table 1). In Group II hypoxia was associated with similar reduction in arterial PO_2, and with hyperventilation which lowered arterial PCO_2 to 20.8 ± 3.3 mmHg and raised arterial pH to 7.62 ± 0.03. In Group II hypoxia-induced increases in CVC in the pons and medulla were blunted whereas those in the cerebral cortex, cerebellum, and spinal cord were abolished (Table 1). A similar degree of hypoxia in Group III (hypocapnia corrected) caused pronounced increases in CVC which were similar to those in Group I (Table 1).

Discussion. The present findings corroborate previous studies indicating pronounced vasodilation in brain during arterial hypoxia under controlled ventilation and attenuation of this response when chemoreceptor-mediated hyperventilation was permitted. Our observation of complete restoration of cerebral vasodilation when normocapnia was maintained during hypoxia in spontaneously breathing dogs is consistent with arterial hypocapnia, rather than a reflex pathway activated by increased lung inflation, blunting cerebral vasodilation. The present study extends previous studies in demonstrating that hypocapnia secondary to chemoreceptor-mediated hyperventilation causes non-uniform antagonism of hypoxic vasodilation in the brain, with greater effect in the cerebral cortex, cerebellum, and spinal cord than in the pons and medulla. Additional studies are planned to ascertain whether this regional variation is influenced by degree of hypoxia or by general anesthetic employed.

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Table 1. Effect of Hypoxia on CVC
(% change from control)

	GROUP I	GROUP II	GROUP III
Cerebral Cortex	$289 \pm 53^{+}$	$39 \pm 29^{*}$	$259 \pm 37^{+}$
Cerebellum	$294 \pm 60^{+}$	$84 \pm 55^{*}$	$288 \pm 25^{+}$
Pons	$375 \pm 51^{+}$	$172 \pm 66^{*,+}$	$456 \pm 45^{+}$
Medulla	$429 \pm 66^{+}$	$206 \pm 42^{*,+}$	$476 \pm 70^{+}$
Spinal Cord	$417 \pm 64^{+}$	$125 \pm 77^{*}$	$501 \pm 53^{+}$

Values are Mean ± S.E. $^{*}P < 0.05$, different from GROUP I; $^{+}P < 0.05$, different from control (normoxic) value.

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Title: MYOCARDIAL OXYGENATION DURING SELECTIVE, GRADED CORONARY HEMODILUTION IN THE WORKING CANINE HEART

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Introduction. Isovolemic hemodilution is increasingly used as a method of blood conservation. Previous studies of the effect of acute hemodilution on myocardial oxygenation utilized systemic replacement of blood with crystalloid or colloid solutions (1). Thus, it was impossible to separate direct effects of hemodilution from effects secondary to increased global cardiac work requirements (2) and activation of cardiovascular reflexes (3). The present study utilized a novel preparation to study direct effects of hemodilution on myocardial oxygenation. Selective, graded reductions in hematocrit were produced in the left anterior descending coronary artery (LAD) of the in situ, working canine heart while measurements of local myocardial oxygen consumption and related parameters were obtained.

Methods. Thirteen large, mongrel dogs were anesthetized with sodium pentobarbital. After intubation and left thoracotomy, the animals were mechanically ventilated with room air supplemented with oxygen. Mean arterial pressure (MAP), mean left atrial pressure (MLAP), and left ventricular pressure (LVP) were measured. LVP was differentiated to give dP/dt max.

The LAD was cannulated just distal to its first major diagonal branch and perfused via an extracorporeal system. The perfusion system utilized two reservoirs; one contained arterial blood with normal hematocrit (HCT) and the other contained arterial blood diluted to a variable extent with lactated Ringer's solution. To cause selective coronary hemodilution, the LAD perfusion field was switched abruptly from the whole blood reservoir to the low HCT reservoir. LAD perfusion pressure was maintained with compressed gas at a level equal to MAP. Coronary blood flow (CBF) via the LAD perfusion line was measured with an electromagnetic flow transducer and meter.

The great cardiac vein was cannulated at same level as the LAD so that the local arteriovenous oxygen content difference ($C(a-v)O_2$) could be determined and used in Fick equation to compute local myocardial oxygen consumption (MVO_2). Measurements of myocardial segment length in LAD bed were obtained with ultrasonic crystals. Percent segment shortening (%SS) was calculated from the formula, %SS = (End-diastolic length - End-systolic length)/ End-diastolic length. Each trial consisted of period of whole blood perfusion followed by period of hemodilution; 1-3 trails were carried out in each animal. Measurements were obtained after attainment of steady-state hemodynamic conditions during selective LAD hemodilution. Dilatory reserve of the LAD bed was assessed from the peak reactive hyperemia following a 90 sec occlusion. Statistical analyses were performed using the Student's t test for paired samples. $P < 0.05$ was considered significant.

Results. Although reductions in coronary hematocrit and oxygen content caused parallel falls in arteriovenous oxygen content difference, increases in coronary blood flow were sufficient to maintain myocardial oxygen consumption constant (Table 1). Graded coronary hemodilution increased progressively peak reactive hyperemic flow, and it reduced progressively dilatory reserve. Percent segment shortening was unaffected by reductions in coronary hematocrit (Table 1).

Under control conditions, values (mean± S.E.) for systemic hemodynamic and arterial blood parameters were unremarkable (MAP, 88± 3 mmHg; MLAP, 4.8± 0.6 mmHg; dP/dt max, 1298 ± 46 mmHg/sec; heart rate, 144± 4 beats/min; PO_2 156± 34 mmHg; PCO_2, 44.0 ± 1.7 mmHg; pH, 7.35± 0.01; HCT, 38.9± 3.1 %). These values remained constant during selective coronary hemodilution.

Discussion. The present study demonstrates well-maintained myocardial oxygenation and function in the face of severe reductions in coronary hematocrit. This was possible because increases in coronary blood flow were sufficient to offset the pronounced reductions in oxygen extraction during coronary hemodilution. Although reduced blood viscosity contributed to these increases in coronary blood flow, a major role was played by local autoregulatory mechanisms which tapped the coronary dilatory reserve. The present findings infer reduced tolerance of myocardium to hemodilution when coronary dilatory reserve is decreased by proximal stenosis, increased metabolic demand, or arterial hypoxemia.

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Table 1. Effects of Coronary Hemodilution

	Control	Reductions in LAD HCT		
		25-35%	15-25%	<15%
	(n=21)	(n=7)	(n=7)	(n=7)
LAD HCT (%)	39.1 ±1.9	29.9* ±1.1	20.3* ±1.3	10.6* ±1.1
MVO_2 (ml/min)	2.33 ±0.17	2.24 ±0.24	2.03 ±0.24	2.25 ±0.15
CBF (ml/min)	37.2 ±3.6	44.2* ±4.6	73.9* ±13.9	127.6* ±13.3
$C(a-v)O_2$ (vol. %)	6.28 ±0.50	5.14* ±0.33	2.94* ±0.37	1.90* ±0.27
%SS	11.7 ±1.1	13.6 ±1.9	12.2 ±2.7	11.3 ±2.1

Values are Mean ± S.E. *$P < 0.05$, different from respective control value.

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Title: GENERAL VS EPIDURAL - WHICH IS THE BETTER ANESTHETIC TECHNIQUE FOR FEMORAL-POPLITEAL BYPASS SURGERY?

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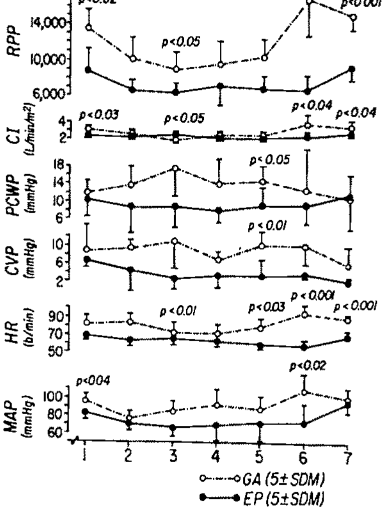
Introduction. Patients with peripheral vascular disease (PVD) involving the lower extremities often have concomitant coronary artery disease, (CAD), and cerebral vascular disease, (CVD). The stress of surgery and anesthesia could exacerbate the patient's underlying cardiovascular disease resulting in a myocardial infarction or cerebrovascular accident in the perioperative period. A common operation for PVD is the femoral-popliteal bypass (FPB). The induction of general anesthesia (GA) may be stressful to the cardiovascular system. The intent of this study was to answer the question: Is regional anesthesia more beneficial in controlling the circulatory responses to surgery?

Materials and Methods. Ten patients requiring FPB were studied. All patients were premedicated with morphine sulfate 0.1 mg/kg IM 90 min before surgery. A radial artery catheter and pulmonary artery catheter were placed in all patients. Patients were randomized into two groups: general anesthesia (GA; N = 5) and epidural anesthesia (EP; N = 5). 4 of the EP patients and 1 GA patient received diazepam (D) 5 mg and 2.5 mg IV, respectively, before placement of indwelling catheters. Patients assigned to GA received thiopental (4 mg/kg IV), lidocaine (1.0 mg/kg IV) for induction, and succinylcholine (1.5 mg/kg IV) for intubation. Anesthesia was maintained with 60% N_2O, 40% O_2, and 1-1.5% isoflurane using mechanical ventilation. 15 min before extubation, the patients received morphine sulfate 0.05 mg/kg IV. The EP group received epidural anesthesia extending to T-10 through the L 4-5 interspace using 3% 2-chloroprocaine (CHL). Additional CHL was administered every 30 min to insure a constant level of anesthesia (average total dose 62 ml/patient). 30 min. after the last dose, morphine sulfate 0.05 mg/kg IV was administered. The epidural catheter was removed before the patient's discharge from the recovery room (RR). The mean arterial pressure (MAP), ECG, heart rate (HR), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), core body temperature and cardiac output were recorded. No patients required supplemental analgesia in the RR. 1: after insertion of indwelling catheters; 2: 5 min after intubation or after reaching T-10, 3:5 min after incision; 4:15 min after femoral artery (FA) clamping; 5:15 min after FA unclamping; 6: 5 min after extubation or last epidural dose; 7: 60 min in RR. No patients in both groups required any supplemental analgesia in the RR. All patients had an ECG in the recovery room. The cardiac index (CI) and rate pressure product (RPP) were calculated. This study was approved by the Institutional Review Board of Columbia University. Written informed consent was obtained.

Results. The number of patient in both groups were equal in incidence for CAD and CVD. The GA patients showed clinically significant increases in MAP, HR, and RPP after insertion of indwelling, 5 min after extubation, and 60 min in the recovery room, respectively, when compared to the EP patients (Fig. 1). Although there were differences between the two groups in CI, PCWP, and CVP at various points throughout the study, they were not clinically significant (Fig. 1). No patient had peri operative ischemic ECG changes or arrythmias. All patients maintained body temperatures of 35-36° C throughout the operation.

Discussion. In patients with CAD, tachycardia has shown to be the hemodynamic abnormality most often associated with perioperative myocardial ischemia. An increase in RPP has also been correlated with perioperative myocardial ischemia (2). Although these observations were made in patients having coronary artery bypass surgery (CAB), many of the patients undergoing FPB have some manifestations of CAD: angina or ischemic ECG changes. During laryngoscopy, myocardial ischemia is as likely to occur in patients undergoing FPB as in CAB surgery. This study demonstrates that emergence from GA can also be stressful to the patient. Pain, shivering, and reaction to the endotracheal tube represents a critical period where cardiovascular instability can occur. Even with adequate analgesia and normothermia, the data for the GA group clearly showed significant increases in MAP, HR, and RPP when compared to the EP group after extubation and in RR. The EP group not only demonstrated greater circulatory stability throughout the operation, but also in RR when the effects of anesthesia would be decreasing. The differences in MAP, CI, and RPP between the GA and EP groups after insertion of indwelling catheters were probably due to the administration of D to most of the EP patients prior to this period. Because of the length of surgery, it is doubtful that this initial dose of D would effect the results seen toward the end of the study. However, these data suggest that during this period, some sedation would be helpful in preventing cardiovascular instability in patients with PVD undergoing FPB regardless of anesthetic technique. These results strongly suggest that epidural anesthesia is a not only a very useful technique for those patients undergoing FPB, but points out the stressful nature of emergence from GA.



Title: THE EFFECT OF ISOFLURANE ON MYOCARDIAL ISCHEMIA IN DOGS DURING CORONARY ARTERY OCCCLUSION

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Introduction. The direct relationship between ischemic heart disease and intraoperative myocardial ischemia and postoperative cardiovascular morbidity indicate the need for detailed knowledge of the effects of anesthetics on myocardial ischemia. Isoflurane decreases global myocardial oxygen consumption but maintains coronary blood flow by producing coronary vasodilation (1); however such vasodilation may impair regional myocardial oxygenation in areas distal to coronary artery obstruction (2). This study was designed to test the hypothesis that isoflurane would improve regional myocardial oxygenation during acute ischemia by reducing regional myocardial oxygen consumption while maintaining or enhancing myocardial oxygen supply.

Methods. Nineteen dogs, 19.3 ± 2.4 kg (SD), were anesthetized with intravenous thiamylal and mechanically ventilated with an air/oxygen blend to maintain normocarbia and normoxia. Catheters were placed into the aorta (AO) and pulmonary artery to measure AO pressure and thermodilution cardiac output (CO). The heart was exposed by a left thoracotomy and the left anterior descending coronary artery (LAD) was encircled with a silastic snare. The LAD and its companion vein were cannulated distal to the snare with 22-ga catheters for pressure measurement and blood sampling for gas tension analysis. A Millar catheter was inserted into the left ventricle (LV) to measure LV pressure and its first derivative (LV dP/dt). The left atrium (LA) was cannulated to inject 15-micron diameter, nuclide-labeled microspheres for calculation of regional myocardial blood flow (RMBF) (3). The epicardial electrogram was measured at 15 sites (3 outside of, 6 at the border of, and 6 within the LAD flow area) to determine the number and distribution of sites with ST elevation over 1 mV and the total magnitude of ST elevation (3). Hemodynamic, RMBF, gas tension, and electrocardiographic data were collected during 2 randomly sequenced periods: normal LAD flow followed by 1) LAD occlusion alone for 15 min and 2) LAD occlusion plus isoflurane (1% inspired) for 15 min; a 1-hr reperfusion period with unobstructed LAD flow elapsed between testing periods. Data obtained during LAD occlusion were compared with those obtained during normal LAD flow; also, data obtained during LAD occlusion with isoflurane were compared with similar data without isoflurane. P less than 0.05 was considered significant.

Results. During LAD occlusion, ST segment elevation increased and cardiac output decreased to the same extent with and without isoflurane. Diastolic AO pressure, LV dP/dt, LV tension-time index, LV stroke-work index, systemic vascular resistance, and normal zone coronary vascular resistance (CVR) were less during LAD occlusion with isoflurane than without it. Neither mean LAD pressure nor CVR in the ischemic zone was decreased by isoflurane during LAD occlusion as compared with no isoflurane. Oxyhemoglobin saturation (O_2 Sat) was not decreased in either the AO or the distal LAD during either LAD occlusion period; coronary vein (CV) O_2 Sat decreased during LAD occlusion without isoflurane (38.2 ± 2.2% vs 25.7 ± 3.2%, $P < 0.05$) but was not significantly reduced during LAD occlusion with isoflurane (34.4 ± 3.3% vs 29.3 ± 2.7%, NS). During both LAD occlusion periods, CV pH decreased and CV PCO_2 increased with LAD occlusion. RMBF in normally perfused areas was unaffected by LAD occlusion with or without isoflurane but the endocardial-to-epicardial RMBF ratio (EN:EP) decreased during both LAD occlusion periods (1.15 ± 0.04 vs 1.06 ± 0.06 without isoflurane and 1.13 ± 0.04 vs 0.98 ± 0.04 with isoflurane, $P < 0.05$ for both). Ischemic zone transmural RMBF was less during LAD occlusion with isoflurane than without it (16.6 ± 3.4 vs 23.1 ± 5.3% of normal, $P < 0.05$). However the EN:EP decreased during occlusion without isoflurane (0.91 ± 0.05 vs 0.68 ± 0.08, $P < 0.05$) but was not significantly less with isoflurane (0.93 ± 0.03 vs 0.80 ± 0.06, NS). Both oxygen supply and consumption in the LAD region were less during the LAD occlusion period with isoflurane than without it (3.5 ± 0.9 vs 8.7 ± 2.7 and 5.3 ± 1.1 vs 10.3 ± 3.1 ml/100 g/min, respectively; $P < 0.05$ for both).

Discussion. In this canine model, isoflurane reduced ischemic zone myocardial oxygen consumption; however, oxygen supply was reduced in parallel. The decreased ischemic zone RMBF with isoflurane may relate to the decreased aortic diastolic pressure, which would decrease the driving pressure for collateral flow into that area; however a shunting of that flow to the normal myocardium was not demonstrated. Electrocardiographic, blood gas tension, or pH evidence of worsened ischemia was not observed with isoflurane.

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Title: NONLINEAR RELATIONSHIP OF ARTERIAL TO PEAK END TIDAL PARTIAL PRESSURE OF CO2 DURING CABG SURGERY

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ABSTRACT

Introduction Continuous monitoring during anesthesia of the peak end tidal partial pressure of carbon dioxide ($ETPCO_2$) has become a widely used method of estimating arterial PCO_2 ($PaCO_2$). Raemer et al (1) demonstrated that arterial minus peak end tidal partial pressure of carbon dioxide (a-$ETPCO_2$) does not remain constant enough in a given patient to allow $ETPCO_2$ to be an accurate predictor of $PaCO_2$ throughout a major operation. To better define the sources of variation between $PaCO_2$ and $ETPCO_2$, we examined a-$ETPCO_2$ in patients undergoing coronary artery bypass surgery. We examined the correlation between a-$ETPCO_2$ and: 1) 5 specific points in the operative procedure, and 2) the parameters of mean arterial pressure (MAP) cardiac index (C.I.) mean pulmonary artery pressure (PAPm), temperature, and shunt (Qs/Qt).

Methods After approval by the Clinical Investigation Committee, 13 patients undergoing elective or emergency coronary bypass surgery without valve replacement were studied. $ETPCO_2$ was measured with an in-line adaptor to an infrared capnometer. All patients had radial arterial and pulmonary arterial catheters. Temperature was measured with the pulmonary artery catheter thermistor. Measurements were made at the same 5 times in all patients: 1) within 5 minutes of induction; 2) within 5 minutes of sternotomy and placement of the chest retractor; 3) immediately prior to going on bypass; 4) within 5 minutes of termination of bypass; and 5) within 5 minutes of chest closure with sternal wires. All blood gases (arterial and mixed venous) were corrected to patient temperature. Newman-Keul multiple sample comparisons were made of the mean a-$ETPCO_2$, MAP, PAPm, temperature, Qs/Qt, and C.I. for all 13 patients at each of the 5 measurement points. Linear regression analysis was carried out to investigate the correlation of MAP, PAPm, temperature, Qs/Qt, and C.I. with a-$ETPCO_2$ in each of the 13 patients.

Results The mean±SD of a-$ETPCO_2$ for the 13 patients ranged from -0.2±0.4 to 5.6±4.6 torr. The mean a-$ETPCO_2$ for all patients at all measurement points was 2.7 torr. Mean a-$ETPCO_2$ and mean C.I. after termination of bypass were significantly greater ($p<0.05$) than the respective means at the other 4 measurement points. Mean Qs/Qt after termination of bypass was significantly greater ($p<0.05$) than the mean after chest closure, the mean prior to going on bypass, and the mean after the chest was opened. There was no consistent correlation between MAP, PAPm, temperature, Qs/Qt, or C.I. and a-$ETPCO_2$ in individual patients.

Discussion As a group, patients undergoing coronary artery bypass surgery have a significantly greater a-$ETPCO_2$ after termination of bypass secondary to increased alveolar dead space from V/Q mismatch and venous admixture. This phenomena is most certainly due to the aberrations in both ventilation and perfusion which occur while on bypass. MAP, PAPm, temperature, Qs/Qt, and C.I. do not serve as good predictors of the integrity of the $PaCO_2$ $ETPCO_2$ correlation in individual patients.

References

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TABLE I

	Post Induct	Ch.open	Pre-CPB	Post-CPB	Ch.closed
1.	1.83±1.85	1.82±2.64	2.62±2.93	5.15±3.8	2.75±3.41
2.	2.09±0.45	2.02±0.96	1.91±0.87	2.71±0.83	2.16±0.44
3.	24.0±6.2	20.1±6.3	19.8±7.3	26.6±5.3	18.7±3.6
4.	75.4±11.9	84.5±7.6	81.4±5.8	78.0±9.1	89.5±9.9
5.	18.2±3.2	20.1±6.9	15.8±3.9	17.6±4.3	18.2±2.4
6.	35.7±0.42	35.1±0.64	34.8±0.72	36.7±0.82	35.6±0.48

1 = a-$ETPCO_2$; 2 = C.I.; 3 = Qs/Qt;
4 = MAP; 5 = PAPm; 6 = Temp.

All values are mean±SD. Unit of measurement for a-$ETPCO_2$, MAP, and PAPm is torr. Qs/Qt is expressed in %. Unit of measurement for temperature is Degree C. Unit of measurement for C.I. is liters/min/m^2.

ANAESTHETIC MORBIDITY: FACTORS OF CLINICAL SIGNIFICANCE

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INTRODUCTION:
Despite considerable strides in recent years, morbidity and mortality still occur in clinical anaesthetic practice with alarming frequency. An earlier study from our institution suggested at least 17.5% of cases were associated with some anaesthetic complication and 0.45% of patients suffered significant morbidity (prolonged hospitalization or permanent debility) from the anaesthetic exposure. This paper examines these non-fatal complications and the factors associated with their occurrences.

METHODS:
A prospective study from 1975 to 1983 provided information on 110,000 anaesthetics administered to adult patients undergoing non-obstetrical procedures. For each anaesthetic, documentation was completed by the anaesthesiologist as to the patient (pre-existing medical illness, age, ASA risk), the anaesthetic technique (drugs, monitors, duration) the surgery (site) and intraoperative and recovery room complications encountered. Post-operative major problems within 48 hours were recorded by an anaesthesia follow-up nurse (the same individual for 9 years) using defined criteria for outcomes. All records were reviewed by the anaesthesia nurse and responsible anaesthesiologist to assure accuracy and completeness. As a validity check and to add demographic information the data base was computer linked to that of the provincial universal health insurance plan.

Each variable was examined as a risk factor for post-operative complications using a chi-square or t-test as appropriate. Significant variables were used to develop a model in a stepwise multiple logistic regression analysis, whereby each variable (patient, surgical, anaesthesia related) was examined after controlling for all others. Odds, ratios and 95% confidence intervals for significant variables ($p<.05$) were determined.

RESULTS:
The proportion of patients with post-operative complications increased with increasing anaesthesia time with a virtual doubling of the frequency for each 60 minutes of exposure. After controlling for all other variables, anaesthesia time of more than four hours remained a strong risk factor for post-operative complications (odds ratio 2.43).

The presence of pre-existing medical conditions or drug use were not associated with increased morbidity but higher ASA risk patients, advancing age and having an intraoperative complication were significant risk factors. Pure narcotic and spinal techniques also placed a patient at higher risk for post-operative complications. As expected, anaesthesiologists with more experiences were less likely to have post-operative complications despite the uniform specialty qualification of the faculty.

CONCLUSION:
Few studies have been published examining the morbidity rates associated with anaesthesia using a prospective epidemiological model. Our results would suggest that the duration of anaesthetic exposure and the experience of the anaesthesiologist may be more significant to the prediction of post-anaesthetic morbidity than had previously been documented. While the patient profile and the surgical procedure performed may influence the intraoperative and recovery room experience, the quantity and quality of "valuable anaesthetic time" remains an important determinant of the patient's recovery and ultimate satisfaction.

Table
RISK OF POST-OPERATIVE COMPLICATION

Variable	Co-Efficient	St. Error	Relative Odds
Time 4 hr / 1 hr	0.89	0.17	2.43 (2.26, 4.74)
Patient ASA 3-5 / ASA 1-2	0.73	0.16	2.08 (1.73, 3.42)
Intra-Op Comp. / No Intra-Op Comp.	1.19	0.19	3.27 (1.53, 2.84)
Spinal/Other	1.69	0.24	5.40 (3.34, 8.71)
Narcotic/Other	0.97	0.17	2.65 (1.40, 3.70)
Increasing Anaesthetist Experience	−0.755	0.43	0.47 (.204, 1.08)

Title: ELDERLY PATIENTS ARE UNDULY SENSITIVE TO PROPOFOL

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Introduction. A study in which thiopental was given by a standard method until a predetermined endpoint (loss of eyelash reflex and consciousness) was reached showed a reduction in dosage in elderly patients (1). Most of this could be accounted for by the physical state of the patients, but Christensen and Andreasen (2) found a statistically significant fall with advancing age in fit subjects. With the new rapidly acting hindered phenol, propofol, undergoing clinical trials it was important to investigate the influence of age on dosage requirements in fit (ASA grades 1 or 2) unpremedicated patients, and to analyse the response of young and elderly subjects to varying bolus doses.

Methods. The study was approved by the regional medical research ethical committee and carried out on 489 patients of either sex who had given informed consent. All injections were made into large antecubital or forearm veins. In the initial dose-finding study, 1.25 mg/kg was given over 20 sec followed by increments of 10 mg at 15 sec intervals until loss of verbal contact occurred. There was a total of 269 patients, with a minimum of 20 in each 10 yr age band from 16 to 80 yr. Multiple regression analysis was used to fit polynomial terms in age to the dose requirements. In the second part of the study groups of 25-30 patients aged under or over 60 yr were given 1.5, 1.75, 2.0 or 2.25 mg/kg over 20 sec and vital signs observed for 2 min.

Results. There was a wide variation in the 'induction' dose of propofol in young patients but the average requirements remained fairly constant until 50-60 yr. In older patients there was less variability in dosage. Most marked was the reduction in the induction dose in patients over 60 yr (Table 1) who required significantly less drug than the younger patients ($P < 0.001$). With this slow rate of administration and lower dosage in elderly patients there were few adverse effects from propofol.

Table 1. Mean (± SEM) induction dose requirements in different age groups.

Age (yr)	n	mg/kg
under 60	187	2.01±0.3
over 60	82	1.64±0.03

Table 2 also shows a marked difference between the response of the two age groups to bolus doses of propofol. At all doses studied most elderly patients were anaesthetised and at this rate of injection both apnea and hypotension were more marked in the elderly. Most important is the fact that with 2.25 mg/kg in younger adults 97% of inductions were acceptable, whereas the comparable dose in the over 60 yr age group was 1.75 mg/kg (100% acceptable). The most marked hypotension and respiratory depressant effect of propofol is very obvious.

Table 2. % response of groups of 30 young (under 60 yr) and 25 older patients to varying bolus doses of propofol.

Dose (mg/kg)	Anesthesia induced		Systolic BP fall exceeding 40 torr		Apnea exceeding 1 min	
years	-60	60+	-60	60+	-60	60+
1.5	53	96	3	12	3	0
1.75	83	100	0	8	3	4
2.0	87	96	0	20	10	20
2.25	97	100	0	45	13	25

Discussion. This study shows the need for caution with propofol in elderly patients, even though they may be considered to be relatively healthy. With experience we have realised the potential dangers of thiopental in the elderly, but there has been no similar definitive study with this established induction agent.

The greater sensitivity to this drug in elderly subjects is very marked and would appear to be greater than with thiopental (3). Bolus doses should be much reduced in patients over 60 yr in whom the injections should be given slowly.

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Title: CLOSED-LOOP FEEDBACK CONTROL OF MUSCLE RELAXATION WITH VECURONIUM IN SURGICAL PATIENTS

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Introduction. We have previously described closed-loop, automated control of muscle relaxation in surgical patients with succinylcholine (1). With software specifically designed using vecuronium pharmacokinetics and dynamics, computer control of relaxation with this drug was compared to manual administration.

Methods. Following Institutional Review Board approval and informed consent, 25 patients were prospectively studied. Patients with neuromuscular disorders or those taking medications affecting the neuromuscular junction were not studied. **Anesthesia:** Premedication with diazepam and cimetidine was followed by induction with thiopental, 2-5 mg·kg^{-1}, I.V. Laryngoscopy was facilitated with succinylcholine, 1 mg·kg^{-1}, I.V., and steady-state anesthetic maintenance was achieved with an end-tidal concentration of 1.0-1.3 MAC of enflurane, measured by mass spectrometry. **Neuromuscular Blockade:** (See figure) Upon receipt of a trigger signal from the controller (computer), a Grass S48 nerve stimulator delivered a supramaximal voltage pulse via a stimulus isolation unit to the ulnar nerve at the elbow. The resulting thenar EMG was amplified, rectified, and integrated by an EMG processor, and the voltage proportional output was displayed digitally on the screen of the EMG processor, and was sampled and held by the controller every 10 seconds. The control EMG signal was displayed as 100, and any depression of the signal was indicated by that percentage of 100 (i.e., 90% depression = 10). The controller was implemented on an S100-based microcomputer equipped with A-D and D-A converters. After the baseline level of EMG was established, the controller executed the program, which employed a proportional-derivative algorithm for vecuronium, determined the infusion rate, and transmitted this signal to an IMED 929 computer-driven infusion pump. Patients were randomly assigned to either the automatic (AUTO) group or the manual (MAN) group. The setpoint (SET) or desired degree of EMG depression for all patients was 90%. In the AUTO group, the controller induced and maintained relaxation until the surgical procedure was completed, whereas in the MAN group, the controller was bypassed and vecuronium was administered by the anesthetist such that 90% EMG depression was induced and maintained, guided by the digital display of the EMG processor. Initially, the patient's name, weight, age, and sex were entered into the controller, and at the conclusion, the times, infusion rates, and percent of control EMG were recorded at 10-second intervals on a floppy disk, along with the patient information. During each study, the force of thumb adduction, slowed EMG, percent of control EMG, and the drug infusion rate were continuously recorded on a Gould four-channel strip chart recorder. **Study Variables:** TIME SET is the number of minutes to achieve the desired level of relaxation; AVE-DEV is the average percent of EMG by which the SET ± 2% was over- or undershot; RELAX-DUR is the duration of at least 50% EMG depression, in minutes; and ADJ-DOSE is the total required dose of relaxant in μg·kg^{-1}·min^{-1}. The data were statistically evaluated, using a two-sample T-test, and differences were deemed significant at a p value of less than 0.05.

Results. Age, weight, and physical status were comparable between the groups. Study variables are presented in the table. The time required to achieve 90% EMG depression was shorter in the MAN group; however, the deviation from the desired level of relaxation was far less in the computerized group.

Discussion. Variability in the response to neuromuscular blockers is well known. This closed-loop, computerized feedback control system for the administration of vecuronium provides a solution to this problem by automatically administering the appropriate dose of drug based on the patient's responsiveness to that drug. In the clinical setting of this study, the system was superior to conventional manual administration in providing the desired degree of neuromuscular blockade in every patient with considerably less over- and underdosage, requiring less drug per unit time. This system was uniformly reliable for long surgical procedures without human interference and its associated deficits and errors. It also demonstrated that smooth control can be nicely achieved with drugs having the kinetics and dynamics of vecuronium.

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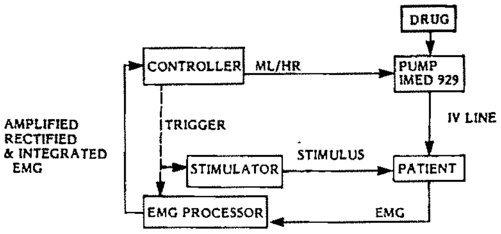

Diagram of the Control System

Comparison of Computerized and Manual Vecuronium Administration Variables (Mean ± SE)

	MAN (n = 11)	AUTO (n = 14)
TIME SET	6.67 ± 0.59	9.30 ± 0.95*
AVE-DEV	1.30 ± 0.18	0.60 ± 0.15+
RELAX-DUR	165.8 ± 18.2	139.3 ± 11.4
ADJ-DOSE	0.62 ± 0.06	0.54 ± 0.06

MAN = manual administration
AUTO = closed-loop feedback control
TIME SET = time to 90% EMG depression, in minutes.
AVE-DEV = average % EMG error per minute > or < SET ± 2%.
RELAX-DUR = duration of > 50% EMG depression
ADJ-DOSE = dose of vecuronium per kg per min relaxation, in μg·kg^{-1}·min^{-1}
* = $p < 0.05$ vs manual administration
+ = $p < 0.01$ vs manual administration

Title: COMPARISON OF THE PROTECTIVE EFFECTS OF ESMOLOL AND FENTANYL DURING LARYNGOSCOPY

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Introduction. The circulatory response to laryngoscopy and intubation can be effectively blunted by low-dose fentanyl (1). This randomized, double-blind study was designed to compare the effects of esmolol, a new, ultra short-acting beta-blocker, with those of placebo and low-dose fentanyl on the circulatory responses to laryngoscopy and intubation in patients of ASA physical status III and IV undergoing noncardiac surgical operations.

Methods. Fifty-four patients undergoing a variety of noncardiac surgical procedures were included. Following Institutional Review Board approval, informed consent was obtained from each patient. Factors necessitating exclusion from study included cardiac dysrhythmia, acute myocardial infarction, arterial hypotension less than 100/50 mm Hg, or the receipt of any beta-adrenergic or calcium-channel blockers within four half-lives of study entry, or of adrenergic augmenting or depleting drugs within six weeks of study entry. Ninety minutes following diazepam premedication, baseline variables were recorded for five minutes. After this, the study infusion was started at time zero. At minute 7, 3 mg of d-Tubocurarine were given intravenously, followed at minute 10 by anesthetic induction with thiopental, 3 to 5 $mg \cdot kg^{-1}$, I.V. Succinylcholine, 1.5 $mg \cdot kg^{-1}$, I.V., was administered simultaneously with the thiopental, and when the patient was fully relaxed, a laryngoscopy lasting at least 30 seconds was performed, followed by endotracheal intubation at minute 11. Anesthesia was maintained with halothane, 0 to 1.5% inspired and nitrous oxide, 60% in oxygen. Both the esmolol and placebo infusions were started at time zero and continued until minute 15, with the esmolol infused at 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 6 minutes and 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ from minutes 7 to 15. The fentanyl infusion was also begun at time zero, at an infusion rate of 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and was completed at minute 10. Arterial pressure and heart rate were measured at one-minute intervals. The control values represent the mean of five baseline measurements; the largyngoscopy values represent the first determination following laryngoscopy; and the post-laryngoscopy numbers are the average of the five values obtained following laryngoscopy. Data was statistically evaluated using one-way analysis of variance, with pair-wise comparisons between means made using the Fisher's protected least significant difference test. Differences were deemed significant at p value less than 0.05.

Results. There were no hemodynamic or demographic differences between groups in the control stage; however, during induction the fentanyl patients received significantly less thiopental than either the esmolol (3.13 ± 0.17 vs 4.05 ± 0.12 $p < 0.01$) or placebo patients (3.13 ± 0.17 vs 3.88 ± 0.17 $p < 0.02$). There were no complications of the study seen in any patient. Hemodynamic data are presented in the following table and the figure.

Discussion. Fentanyl, in the dose employed here, was associated with the lowest heart rates and mean arterial pressures, both during and following laryngoscopy. During laryngoscopy, the esmolol infusion resulted in heart rates higher than the control, but significantly lower than in the placebo group. Esmolol was also associated with unchanged mean arterial pressure, which was significantly higher than that seen with fentanyl. This means that fentanyl, while preventing the tachycardic rise in myocardial oxygen consumption, may decrease coronary perfusion pressure. Esmolol, on the other hand, only attenuated the heart rate increase, while myocardial perfusion pressure was apparently preserved. It is conceivable that the combination of esmolol with a smaller fentanyl dose may offer the advantages of both drugs.

Reference.

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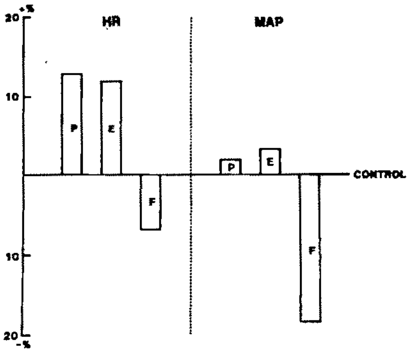
HEMODYNAMIC RESPONSES DURING AND FOLLOWING LARYNGOSCOPY (MEAN ± SEM)

		Cont	Laryng	Post
HR	P	79.6 ± 1.5	89.8 ± 3.4*	89.1 ± 1.4*
	E	70.6 ± 1.1	79.1 ± 3.5*‡	76.6 ± 1.1*‡
	F	78.7 ± 1.5	73.2 ± 3.9*‡	66.0 ± 1.5*+‡ §
MAP	P	101.1 ± 1.6	103.1 ± 5.6	105.6 ± 2.5*
	E	103.6 ± 1.2	107.0 ± 5.0	101.9 ± 1.9
	F	103.9 ± 1.8	84.5 ± 6.2*‡ §	79.8 ± 1.9*‡ §

P = placebo; **E** = esmolol; **F** = fentanyl
Cont = control; **Laryng** = laryngoscopy;
Post = post-laryngoscopy
HR = heart rate in beats • min^{-1}
MAP = mean arterial pressure in mm Hg
* = $p < 0.05$ vs control in same group
+ = $p < 0.05$ vs laryngoscopy stage in same group
‡ = $p < 0.05$ vs placebo group at same stage
§ = $p < 0.05$ vs esmolol group at same stage



Changes in Heart Rate (HR) and Mean Arterial Pressure (MAP) During Laryngoscopy
P = Placebo; E = Esmolol; F = Fentanyl
Absolute values and statistical significance are present in the table.

Title: MIDAZOLAM AS AN ADJUNCT TO MEPERIDINE FOR POSTOPERATIVE ANALGESIA

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Introduction: Anxiety is believed to play an important role in the patient's perception of postoperative pain (1). Midazolam is a recently introduced benzodiazepine with demonstrated anxiolytic and sedative properties and has been successfully used as an intramuscular premedicant (2). We sought to determine its efficacy as an adjunct to IM Meperidine in the treatment of pain following upper abdominal surgery.

Methods: One hundred and fifty male and non-pregnant female patients, ASA physical status I or II, aged 18-65 years, weighing 50-100 kg gave their informed consent to participate in this institutionally approved study. All were scheduled to undergo upper abdominal surgery. Known drug or alcohol abusers, those on chronic sedative, tranquilizer or analgesic therapy were excluded. Each patient was randomly assigned to one of five groups of 30 patients, to receive postoperative pain medication as follows: 1. Meperidine (MEP) 0.5 mg/kg + Midazolam (MID) 0.05 mg/kg; 2. MEP 1.0 mg/kg + MID 0.05 mg/kg; 3. MEP 0.5 mg/kg; 4. MEP 1.0 mg/kg; 5. MEP 1.5 mg/kg. In all cases, injection volume was made up to 2 ml with placebo (MID vehicle). In order to enter the study, on the morning following surgery a patient had to describe their pain as moderate or severe on a scale that included mild and none, and not have received any analgesic or sedative medications within the previous 3 hours. The single injection was then given IM, double blind, into the vastus lateralis muscle. Patients with inadequate pain relief, requiring analgesics within 1 hour of the test injection, were excluded from further study, not included in the analysis of results and were replaced. At 0, 30, 60, 120, 180, 240, 300 and 360 minutes following injection, analgesia, sedation, anxiety and vital signs were assessed. Pain was evaluated (PNEVAL) by a nurse observer on a scale of 4 (very severe) through 0 (none). Each patient evaluated their pain intensity score (PIS) on a visual analogue scale (0-100, where 0=no pain, and 100=worst pain imaginable), and pain relief (PNREL) on a scale of 4 (no relief) through 1 (complete relief). Patient anxiety was measured prior to and at 30, 60 and 120 minutes after, injection, using a State-Trait Anxiety Inventory (STAIX) (3) Also at these times, memory cards were randomly shown and recall was determined next day. Sedation was evaluated (SEDEVAL) by the nurse on a scale of 6 (hyperactive) through 1 (asleep, no response). Patients with inadequate relief of pain between 60 and 360 minutes, were given additional analgesics and the data collected prior to rescue was included in the analysis of results. Comparisons among the groups were made using repeated measures analysis of variance (RMANOVA); $p < 0.05$ was considered as significant. For the statistical analyses of PNEVAL, PNREL and PIS, at each measurement point after 60 minutes, group sizes were made up to 30 by assuming that those patients who had dropped out, would have a PNEVAL score of 3, a PNREL score of 4 and a PIS score equal to that on entering the study. Sedation scores could not be so corrected and therefore RMANOVA could only be applied at times 0, 30, 60 minutes.

Results: Demographics were similar among the five groups and over 80% of patients underwent biliary surgery. Survival analysis showed no statistically significant differences among the five groups in the time intervals until remedication, although at any measurement point group 2 always had the most patients. Assessments of pain (PNEVAL, PIS) suggested that group 2 had the greatest analgesia but statistically, group 2 was only significantly superior to group 3. Two hours post medication and at all subsequent observation times, group 2 had significantly more pain relief (PNREL) than group 3. Group 2 was significantly more sedated (SEDEVAL) than 3, 4 and 5 at 1 hour. Group 2 was the least anxious (STAIX) but only significantly different from group 3, at 30 minutes. There was significant correlation between pain scores and SEDEVAL scores at 30 and 60 minutes. When average PNEVAL scores were covaried with SEDEVAL scores, there were no significant differences in PNEVAL among any of the groups. Incidence of anterograde amnesia (memory cards) was significantly greater in groups 1 and 2 (MID), than 3, 4, 5 (MEP) at 30 minutes ($X^2=17.1$, $p<0.02$) and 60 minutes ($X^2=18.72$, $p<0.001$) but not at 120 minutes. There were no significant changes in vital signs, nor were there any notable side effects in any of the groups.

Discussion: The analgesic effect of meperidine was not significantly enhanced by addition of midazolam. This finding is at variance with that reported (4) using similar combinations of morphine with midazolam and may be attributed to pharmacologic differences between morphine and meperidine.

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Title: MONITORING NEUROMUSCULAR BLOCKADE: EMG VS TWITCH TENSION
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Introduction: Monitoring of neuromuscular blockade is important whenever muscle relaxants are used. Traditionally it involves stimulating a peripheral nerve and observing and/or recording the evoked mechanical response. Mechanical recordings present certain technical difficulties such as the direction of the applied force, and the resting tension of the muscle. Electromyographic (EMG) techniques offer fewer difficulties but until recently have not been available for clinical use in the OR. The purpose of this study was to compare the results of integrated EMG monitoring, using the Datex 221 Neuromuscular Transmission Monitor (NMT) (Puritan Bennett Corp, Wilmington, Mass) with twitch tension monitoring, during the onset of neuromuscular blockade produced by curare.

Methods: Eleven patients gave their informed consent to participate in this institutionally approved study. None had a history of disordered neuromuscular function. All received oral diazepam as premedication. On arrival to the operating room, NMT skin electrodes were applied to the patient's left wrist and hand. Two (stimulating) electrodes were placed over the ulnar nerve, two (recording) electrodes over the hypothenar muscles, and one ground electrode, in the palm of the hand. The left arm was then placed in a specially constructed armboard so that twitch tension in the adductor pollicis muscle could be measured using a force transducer (Grass FT10) and recording polygraph (Grass 79D). Resting tension in the thumb was set at 200-300 gm force. Anesthesia was induced with thiamylal sodium 150-200 mg iv, fentanyl 50 mcg; and maintained with N_2O/O_2 (70/30%). Once the patient was asleep, the NMT was calibrated to produce a supramaximal stimulus which evoked maximal EMG and mechanical responses. The unit then delivered trains-of-four stimuli (2Hz; stimulus duration 0.10 msec) to the ulnar nerve every 20 seconds. Following calibration, curare in increments of 3-6 mg was administered iv and the responses observed. When relaxation was adequate, the patients were intubated and the anesthetic proceeded as usual. Succinylcholine and the potent volatile agents were avoided. EMG responses were read directly from the NMT's digital display of T_1/Control (%) and T_4/T_1 (%). Mechanical responses were measured from the polygraph tracing. EMG responses were compared with simultaneously recorded mechanical responses using linear regression analysis.

Results: Twelve pairs (EMG and mechanical) of responses were selected from each patient during onset of curarization. The results are shown in Figure 1 (T_1/C), and Figure 2 (T_4/T_1). EMG ratios are shown on the y-axis. The analysis for T_1/C is expressed by the equation: $y=0.53x + 37$; $r=0.72$; Sy.x (standard error of the estimate)=17.2; $t=11.51$; $P<0.001$. The analysis for T_4/T_1 is described by: $y= 0.76x + 25$; $r=0.78$; $Sy.x=16.8$; $t=13.9$, $P <0.001$. The hatched lines in each figure indicate the 95% confidence limits of the regression equations.

Discussion: Differences between the results of mechanical and EMG monitoring of neuromuscular blockade have been reported previously (1) but have not been quantified. Our results show that there is a fairly good correlation between the ratios obtained using NMT (EMG) and twitch tension monitoring. In monitoring T_1/C during onset of curarization, the electrical is more sensitive than the mechanical response, showing a decrease in ratio before it is seen in the mechanical response. In the presence of a profound block, when T_1 is just below the threshold of mechanical detection, the EMG T_1/C is 37%. The EMG can thus be used to monitor more intense neuromuscular blockade (EMG T_1/C 0-37%). Decreases in the T_4/T_1 (fade) ratio, however, are detected earlier in the mechanical response than by EMG. The reasons for the differences in the results observed using the two monitoring methods remain unclear. However, once familiarity is gained with the NMT, its electromyographic system certainly simplifies routine clinical monitoring of neuromuscular transmission.

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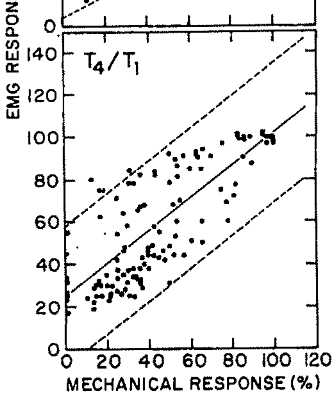

Title: HEMODYNAMIC EFFECTS OF NEUROMUSCULAR BLOCKERS IN CONTROLLED HYPERTENSIVES: A RANDOMIZED STUDY

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Introduction. Controversy continues regarding anesthesia risks and associated blood pressure changes in hypertensive patients (pts). Their blood pressure is more labile compared to normotensives, and they are prone to frequent hypo- and hypertensive episodes during surgery (1). Controlled (treated) hypertensives are as predisposed to peri-op blood pressure fluctuations as untreated pts (2). We performed this study to examine hemodynamic effects of neuromuscular blockers during anesthesia in controlled hypertensives and normotensive pts.

Methods. With informed consent, we studied 2 groups of pts undergoing coronary bypass surgery. None had valvular, renal, hepatic or neurologic disease. Group I consisted of 20 normotensive pts without history of hypertension; Group II were 20 pts with confirmed history of hypertension and BP controlled to < 140/90 before surgery. Pre-op beta adrenergic and calcium channel blockade were continued to morning of surgery. Premedication was morphine sulfate 0.1 mg/kg IM, scopolamine 0.4 mg IM, and transdermal nitroglycerin 5 or 10 mg. Pts within each group were randomized to receive equipotent doses (0.12 mg/kg) of either pancuronium (P) or vecuronium (V) given at induction with fentanyl 50 mcg/kg and 100% O_2. Hemodynamics were measured preinduction (control), 2 min after induction, 2 and 5 min after intubation. Paired comparisons were made by a student t-test with $P < 0.05$ as significant.

Results. The study groups were comparable for age, pre-op myocardial infarction, degree of coronary disease, pre-op beta adrenergic and calcium channel blocker therapy, and baseline hemodynamics, including systolic, diastolic and mean arterial pressures.

Cardiovascular responses are summarized in the tables 1 and 2. V permitted stable hemodynamics in normotensive and hypertensive pts, with minimal (< 5%) HR and BP changes over baseline at all measurement times. In contrast, P caused tachycardia in both pt groups; HR was significantly higher ($P < 0.001$) than with V at all measurement times in normotensive and hypertensive pts. Systolic BP also increased more after intubation with P when compared to V in the hypertensive group (5% vs −1%, $P < 0.05$). Other hemodynamic measurements did not show significant differences between groups. No ischemic changes were noted on EKG.

Discussion. Our study illustrates that appropriate selection of neuromuscular blocker can influence cardiovascular responses to induction and intubation in controlled hypertensives. P caused the expected tachycardia due to its vagolytic effects. V, which does not release histamine or show autonomic effects, permitted stable hemodynamics in controlled hypertensives and normotensive patients. This is contrary to the previous observations of Roberts (1) and Goldman (2). Other factors which may have contributed to this stability are: A) beta adrenergic and calcium channel blockade were used to control BP and were continued to the morning of surgery. These agents differ from "rauwolfia" and ganglion blocker agents that can cause severe hypotension. B) Fentanyl anesthesia, which minimizes cardiovascular responses to induction and intubation. We conclude that pre-op BP control in hypertensives, and selection of drugs free of cardiovascular effects, can provide stable induction of anesthesia which is comparable to that observed in normotensive patients.

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TABLE 1: HEMODYNAMIC MEASUREMENTS WITH VECURONIUM (M ± SE)

		Control	2 min after induction	2 min after intubation	5 min after intubation
HR	Norm.	71 ± 5	69 ± 5	73 ± 6	65 ± 6
	Hyper.	65 ± 5	61 ± 4	62 ± 4	60 ± 4
MAP	Norm.	100 ± 3	103 ± 7	106 ± 6	104 ± 5
	Hyper.	98 ± 8	95 ± 9	98 ± 8	94 ± 8
CI	Norm.	2.5 ± 0.1	2.5 ± 0.2	2.7 ± 0.2	2.5 ± 0.2
	Hyper.	2.8 ± 0.3	2.7 ± 0.2	2.8 ± 0.2	2.8 ± 0.2
CVP	Norm.	8 ± 1	10 ± 1	10 ± 1	9 ± 1
	Hyper.	9 ± 2	9 ± 1	10 ± 1	9 ± 1
PCWP	Norm.	14 ± 2	19 ± 4	19 ± 3	18 ± 2
	Hyper.	13 ± 1	13 ± 1	14 ± 1	13 ± 1
SVR	Norm.	1534 ± 108	1569 ± 165	1550 ± 181	1627 ± 135
	Hyper.	1473 ± 269	1333 ± 147	1300 ± 118	1262 ± 122

TABLE 2: HEMODYNAMIC MEASUREMENTS WITH PANCURONIUM (M ± SE)

		Control	2 min after induction	2 min after intubation	5 min after intubation
HR	Norm.	63 ± 5	77 ± 7*	80 ± 7*†	74 ± 6*
	Hyper.	71 ± 5	86 ± 5*	89 ± 5*†	85 ± 5*
MAP	Norm.	95 ± 5	95 ± 4	101 ± 5	96 ± 5
	Hyper.	96 ± 5	93 ± 4	104 ± 5	101 ± 5
CI	Norm.	2.9 ± 0.3	3.0 ± 0.3	3.0 ± 0.4	2.9 ± 0.3
	Hyper.	2.8 ± 0.3	3.2 ± 0.3	3.2 ± 0.2	3.2 ± 0.2
CVP	Norm.	9 ± 1	8 ± 1	8 ± 1	7 ± 1
	Hyper.	10 ± 1	11 ± 1	11 ± 1	10 ± 1
PAD	Norm.	15 ± 2	16 ± 1	16 ± 1	15 ± 1
	Hyper.	13 ± 2	16 ±.3	15 ± 2	14 ± 2
SVR	Norm.	1261 ± 79	1257 ± 121	1354 ± 165	1350 ± 161
	Hyper.	1274 ± 107	1072 ± 100	1175 ± 101	1158 ± 104

Abbreviations: HR: Heart rate (beats/min); MAP: Mean arterial pressure (mm Hg); PAD: Pulmonary artery diastolic (mm Hg); PCWP: Pulmonary capillary wedge pressure (mm Hg); CVP: Central venous pressure (mm Hg); CI: Cardiac index (ml/min/m^2); SVR: Systemic vascular resistance (dynes/sec/cm^{-5}); Norm: Normotensive; Hyper: Hypertensive

* $P < 0.05$ when compared to V as percent change over baseline at the measurement time indicated.

† $P < 0.05$ when compared as percent change over baseline for the same drug.

Title: AMIODARONE AND GENERAL ANESTHESIA - A RETROSPECTIVE ANALYSIS

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Introduction Amiodarone hydrochloride (AH) is a benzofuran derivative introduced 17 years ago as a vasodilator for anginal therapy. Recently, AH has been utilized primarily as an antiarrhythmic agent (1). It has been found to be highly effective in the treatment of chronic ventricular tachycardia (VT) refractory to other antiarrhythmic regimens. AH has been reported to cause hypotension and bradycardia during general anesthesia (2). A retrospective analysis was performed on 33 patients on chronic oral AH who presented for intraoperative electrophysiologically (EPS) guided endocardial resection and aneurysmectomy.

Method From 1978 to 1983, 129 patients underwent EPS-guided resection and aneurysmectomy. Of these, 33 were on oral AH therapy to within 25 days of surgery. The charts and anesthetic records of all 129 patients were evaluated for demographic and preoperative data, operative course, anesthetic technique, post-bypass and intensive care unit (ICU) course including postoperative (postop) complications. The 33 AH patients comprised group I and the 96 other patients group II. All data was evaluated by student's t-test and chi-square analysis.

Results Preoperative and intraoperative data for group I and group II patients are summarized in Table #1. Table # 2 shows the cardiovascular support required post-bypass and in the ICU. No significant difference in postop incidence of VT, bleeding, sepsis, or renal complications was observed. However, 21% group I patients developed respiratory complications as opposed to 4% of the group II ($p < .05$). 93% group I patients were extubated with a mean time of 76 hours postoperatively and 92% group II patients were extubated postoperatively with a mean time of 30 hours ($p < .05$). 3 of 33 group I patients expired (1 of arrhythmia, 1 of sepsis, 1 of pump failure) while 12/96 group II patients expired (3 of arrhythmia, 1 of respiratory complications, 7 of pump failure and 1 of sepsis).

Discussion The results show that the group I patients began with decreased ventricular function, and that the group I perioperative course was more complicated, requiring greater cardiovascular support both post-bypass and in the ICU. The increased need for catecholamine and vasodilator support in the ICU and the greater time to extubation in group I reflects the stormier (postoperative) course of patients. The increased incidence of respiratory complications could be explained by the complicated ICU course, increased duration of intubation or possibly by the pulmonary toxicity of the AH itself. As AH has both alpha- and beta-blocking properties and can cause decreased diastolic depolarization and increased action potential duration, it is not surprising that bradycardia and hypotension can be seen with its use (3) In conclusion, patients on preoperative oral AH for control of refractory ventricular arrhythmias demonstrated greater need for post- bypass and ICU inotropic and vasodilator therapy, as well as longer time to extubation.

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Table #1

	Group I (amiodarone)	Group II (non-amiodarone)
Number	33	96
Age (years)	56	57
sex	31 male 2 female	74 male 22 female
weight (kilograms)*	75	75
height (centimeters)*	177	172
body surface are (meter^2)*	1.9	1.9
LVEDP (mm mercury)*	23.0†	18.5
cardiac output (l/min)*	4.8	4.6
preoperative sinus rhythm	91%	94%
atrial fibrillation	3%	3%
preoperative transvenous pacemaker rhythm	6%	3%
fentanyl	27††	40
morphine	0	2
isoflurane	4††	3
enflurane	0††	21
halothane	2††	30

* all values are expressed as mean of the group
† $p < 0.05$
†† $p < 0.001$

Table #2 Cardiovascular Support

	Group I	Group II
Neosynephrine (mg on bypass)	4.8*	2.9
epinephrine (% patients on post bypass infusions)	87*	33
Vasodilators (% patients on post bypass infusions)	72*	44
intra-aortic balloon pump insertion post bypass (% patients)	39	25
epinephrine in SICU (% patients received infusion)	81*	50
Nitroprusside in SICU (% patients received infusion)	66*	44

* $p < 0.05$

Title: THE EFFECT OF FENTANYL ON MYOCARDIAL SALVAGE IN DOGS AFTER CORONARY ARTERY OCCLUSION

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Introduction. Large doses of the synthetic narcotic, fentanyl (50 to 100 µg/kg), frequently are administered clinically to patients undergoing cardiac surgery, because of the hemodynamic stability and obtundation of the sympatho-adrenal stress response to surgical stimulation that is provided by high concentrations of narcotics. However, fentanyl does not alter ischemic myocardial oxygen utilization and has minimal effects on canine coronary artery adrenergic function. This study examined the effect of fentanyl on myocardial infarct size (MIS) and on regional myocardial blood flow (RMBF) after coronary artery occlusion in dogs.

Methods. Thirteen adult mongrel dogs (21.1 ± 2.5 kg) were anesthetized with thiamylal, 15 mg/kg iv, plus 2-4 mg/kg/hr. Controlled ventilation was applied with an air/oxygen mixture to produce normocarbia and normoxia and acid-base balance was maintained with sodium bicarbonate. Lead II of the ECG was monitored continuously. Catheters were placed into the pulmonary artery (PA), the left ventricle (LV), and the aorta to measure corresponding pressures and thermodilution cardiac output (CO) and to sample blood for gas tension analyses. The heart was exposed by a left fifth interspace thoracotomy, and the left anterior descending coronary artery (LAD) was dissected free and encircled immediately proximal to the first major apical diagonal branch with a ligature. The left atrium (LA) was cannulated for subsequent injection of 15 µ-diameter, nuclide-labeled microspheres for RMBF measurement (1). Hemodynamics were recorded and the first set of microspheres was injected before LAD occlusion. Lidocaine (1.5 mg/kg iv) was injected and the LAD was occluded permanently. Five minutes later, macroaggregated albumin microspheres labeled with 0.5 mCi/kg of ^{99m}Tc were injected into the LA to measure by autoradiography the area of myocardium that was hypoperfused and thus at risk of infarction (2). One hour after LAD occlusion, microspheres were again injected and hemodynamic data were collected, after which the dogs were randomly assigned to receive continued thiamylal infusion either alone (controls) or in combination with fentanyl, 100 µg/kg iv bolus. Hemodynamic data and arterial blood gas tensions were recorded hourly thereafter for 6 hr. RMBF measurements were repeated at 3 and 6 hr after LAD occlusion. After 6 hr, the dogs were sacrificed. The hearts were removed and the LV cut into 5-mm thick sections, which were stained with tetrazolium (1). The autoradiographic image of each section was digitized to quantify the area of myocardium hypoperfused 5 min after LAD occlusion. The tetrazolium-stained sections were digitized to quantify the area of histochemical infarction, after which the infarcted tissue was dissected from normal tissue and weighed for a direct MIS determination. RMBF was calculated from endocardial and epicardial segments of the normally perfused, the ischemic, and the infarcted zones. Differences between groups were assessed by using Student's *t* test and analysis of variance. Results are expressed as mean ± SE.

Results. By the randomization, 6 dogs received fentanyl and 7 did not. Arterial blood gas tensions and pH did not differ between the two groups. Mean arterial pressure decreased in control dogs (from 123 ± 6 to 83 ± 8 mmHg) but did not change with fentanyl (112 ± 7 vs. 99 ± 6 mmHg) from before LAD occlusion to 6 hr after occlusion ($P < 0.05$). No significant differences in MIS were seen between the groups (19.0 ± 6.1 and 26.1 ± 3.9% of LV with and without fentanyl, respectively), or for the area at risk of infarction (37.8 ± 4.2 and 34.1 ± 7.7% of LV, respectively). However, the difference between infarcted area and hypoperfused area at risk, which we used as a measure of myocardial salvage, was 6 ± 4.1% without fentanyl and 18 ± 6.1% with fentanyl ($P < 0.1$). RMBF values decreased in ischemic zones after LAD occlusion but did not differ significantly between the two groups after occlusion.

Discussion. The principal finding of this study is that neither RMBF nor MIS was altered by a 100 µg/kg-fentanyl bolus in this canine model of acute myocardial infarction produced by LAD occlusion. There appeared to be a small increase in myocardial salvage with fentanyl although this was not highly statistically significant. Further studies are required to delineate the mechanisms of this salvage.

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Title: SOMATOSENSORY-EVOKED POTENTIALS FOR THE EVALUATION OF ANALGESIC PROPERTIES OF NALBUPHINE IN MAN

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Introduction. The fundamental difference between clinically useful types of agonist-antagonists is conceived that one produces analgesia by acting on the µ-opioid receptor and the other by acting on the kappa-receptor (1). Nalbuphine, a mixed agonist-antagonist, 0.5-0.8 the potency of morphine, with low abuse potential and a ceiling effect for respiratory depression (2,3), was evaluated in regard to its effects on somatosensory-evoked potentials (SEP). Together with pain report, amplitude and latency changes of event related potentials, SEP's are a good measure for the individual pain perception rather than just transduction and transmission of stimulus events (4). Thus increasing doses of the narcotic antagonist were evaluated for SEP-effects and their correlation with pain threshold.

Methods. Following institutional approval for human investigation and informed consent by the subjects, increasing doses of nalbuphine (50-100-500-1000 µg/kg) were given to 20 volunteers i.v. every 15 min. Before and after each injection, SEP's and tolerance threshold to increasing electrical stimulus intensities where strong pain was experienced were assessed. Evoked potentials were induced by right median nerve stimulation, which was of square wave nature with a duration of 0.2 ms, at a rate of 5/s, a stimuli repetition of 1024, and a current twice above motor threshold (supramaximal). Potentials were derived from position FpZ-C_3 (reference right ground arm strap) after having passed an isolated high gain amplifier and a filter setting between 5-800 Hz. At a sampling rate of 256 KHz, the potentials were averaged a period of 150 ms (Neurotrec, Interspec Medical Wisconsin) and the display analysed by cursor position in terms of base to peak amplitude (µV) and latency (ms) at each of the major deflection changes identified in terms of polarity (N= negative). To determine significance the effects were compared to control using the Friedman and Wilcoxon-Wilcox test.

Results. Compared to control a total of 650 and 1650 µg/kg of nalbuphine induced a significant ($p < 0.01$) increase in latency of the N_{40}- and the N_{100}-peak (table). The increase in latency showed a good correlation (r=0.93 and 0.94 respectively) with the tolerance to increasing stimulus intensities (mA, table). In some instances a total dose of 150 µg/kg revealed a similar increase in latency as 1650 µg/kg. Increase in latency was marked after 650 µg/kg suggesting a ceiling effect. Amplitude changes of the three components N_{20}, N_{40}, and N_{100} were not significant when compared to control (table).

Discussion. SEP-latency changes of the late N_{100}-peak after nalbuphine correlate well with subjective painfulness (tolerance threshold). Contrary to morphine, an opioid purportedly interacting with the µ-opioid receptor, which suppresses the amplitude of the N_{120}-peak (5), nalbuphine increases latency suggesting a different mode of action accompanied by a decrease in the velocity of nervous conduction. Since late evoked potentials are generated in the thalamocortical projections which are also related to subjects cognitive activities (4) it is postulated that nalbuphine exerts its analgesic activity mainly through modulation of impulses running along the extralemniscal sensory system. It is responsible for the mediation of the timeless, bothering and conflicting feelings associated with pain. In regard to dose-efficacy a total of 650 µg/kg of nalbuphine seems to present ceiling effects.

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dose	N_{20}		N_{40}		N_{100}		
µg/kg	ms	µV	ms	µV	ms	µV	mA
control	23.8 ± 0.8	1.5 ±0.4	42.4 ± 1.5	1.2 ±0.3	89.1 ± 2.8	1.2 ±0.2	13.8
50	23.9 ± 0.9	1.3 ±0.2	43.2 ± 1.6	1.5 ±0.4	93.0 ± 3.2	1.3 ±0.2	14.6
100	23.6 ± 0.8	1.6 ±0.3	42.9 ± 1.4	1.4 ±0.4	94.2 ± 3.9	1.3 ±0.2	18.2
500	23.4 ± 0.8	1.3 ±0.3	43.7 ± 1.5	1.5 ±0.4	98.3 ± 4.0	1.1 ±0.2	21.7
1000	23.7 ± 0.9	1.7 ±0.5	46.1 ± 1.6	1.7 ±0.4	103.7 ± 4.5	1.6 ±0.6	23.5

(n = 20; mean ± SEM)

Title: REPRODUCTIVE AND TERATOGENIC EFFECTS OF FENTANYL IN SPRAGUE-DAWLEY RATS

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Introduction: In the past, we have studied Swiss-Webster mice and Sprague-Dawley rats to determine if halothane, methoyflurane, enflurane, isoflurane and nitrous oxide caused adverse reproductive or teratogenic effects.[1-8] Our most significant findings were that: 1) 75% nitrous oxide in rats led to increased fetal wastage and to major and minor developmental anomalies; and 2) 0.6% isoflurane in mice, but not in rats, resulted in an increased incidence of cleft palate. In the present study, we examined the effects of three different fentanyl dosages on reproduction. To obtain the highest possible fentanyl plasma levels without causing respiratory depression, fentanyl was administered continuously using chronically implanted, osmotic minipumps.

Methods: 155 virgin female Sprague-Dawley rats were randamly divided into 5 groups: 1) control (n=43; water in pump); 2) positive control (n=28; retinoic acid; 20 mg/kg, p.o. on days 10-12); 3) fentanyl, 10 ug/kg/day (n=28; low dose); 4) fentanyl, 100 ug/kg/day (n=28; medium dose); 5) fentanyl, 500 ug/kg/day (n=28; high dose). Using general anesthesia, an Alzet osmotic minipump with a 15 day drug supply was implanted subcutaneously in the back of each rat in groups 1,3,4 and 5. Dosage selection was based on data from preliminary studies with minipumps in which doses greater than 500 µg/kg/day resulted in maternal mortality and failure to gain weight. Plasma fentanyl level at an infusion rate of 500 µg/kg/day is 12 ng/ml. After two weeks, covering almost three full ovarian cycles, the pump was removed and replaced with another containing a 29-30 day drug supply. Breeding was started the day after pump replacement. One untreated male rat was placed with four females, nightly, for eight nights. The day sperm were observed in the vagina was defined as day one of pregnancy. On day 21 of pregnancy, each dam was killed, and the uterus was examined to determine the number of live and dead fetuses and resorptions. Each fetus was weighed and examined externally. Every other fetus was fixed in Bouin's solution, sectioned and examined microscopically for visceral abnormalities. The remaining fetuses were cleared in KOH and the skeletons stained with Alizarin red S and examined for abnormalities. Arterial blood gas measurements were made in nonpregnant rats from each group. All examinations were done without knowledge of the treatment groups. Data were analyzed by ANOVA and by Student's T test, corrected for multiple analyses, when difference were found with ANOVA. $P < 0.05$ was considered significant.

Results: 4 of 28 rats in the high dose group died within 24 hours after implntation of the first pump. No other treatment-related adverse side effects occurred in the study. Rats in all groups gained similar amounts of weight during pregnancy and blood gas values were in the normal range. There were no differences among the groups in reproductive indicies and fetal morphological examinations failed to demonstrate any adverse treatment effects (Table).

Discussions: There are no published reports of the reproductive and teratogenic effects of fentanyl. To our knowledge, the only other similar study was the unpublished, 1966 evaluation by Janssen Pharmaceutica carried out for the purpose of FDA submission. In this study bolus doses of fentanyl, up to 1250 µg/kg, s.c. and 30 µg/kg, i.v.,were administered. In our pilot studies, rats administered these fentanyl doses developed board-like rigidity and most ceased breathing and died unless they were stimulated. Blood gas values in surviving rats were consistent with severe respiratory acidosis. Thus the many deaths observed in the Janssen study at high dosages and the decreased fertility and increased resorptions probably were secondary to the abnormal maternal respiratory physiologic effects. In the present study, none of the fentanyl doses produced adverse repoductive or teratogenic effects. The highest dose, 500 µg/kg/day, was associated with a maternal toxic effect within 24 hours after the first pump was implanted but there was no further morbidity or mortality in the study. In fact, blood gas values in non-pregnant members of all groups were normal and respiratory depression did not occur at any dosage in pregnant rats. In summary, we evaluated the reproductive and teratogenic effects of three doses of fentanyl with the highest dose well above that administered patients having cardiac surgery. From this we conclude that fentanyl is devoid of adverse reproductive and teratogenic side effects. We also conclude that osmotic minipumps facilitate the study of narcotics as they allow delivery of doses that ordinally would not be tolerated without producing adverse respiratory effects.

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Table. Reproductive and Morphologic Data

		Pos.	Fentanyl dose		
Treatments	Cont.	Cont.	Low	Medium	High
Starting no. of dams	43	28	28	28	28
Overall pregnancy rate (%)	84	64	93	54	75
No. of dam exam. at C-sec	34	17	25	15	18
Starting dam weight (g)	215	214	215	215	215
Weight gain during preg. (g)	130	53*	128	124	131
No. of corpora lutea	12.8	14.1	13.0	14.5	13.4
No. of implantations	11.3	11.9	11.7	11.5	11.8
No. of resorptions	0.2	10.0*	0.6	0.2	0.6
No. of live fetuses/litter	11.1	1.8*	11.1	11.3	11.2
% female	44	33	56	50	49
Live/implantations (%)	98	15*	93	98	92
Mean fetal weight (g)	4.0	2.9*	4.0	4.0	4.0
No. of fetuses examined					
External	377	30	277	170	202
Visceral	188	15	136	84	102
Skeletal	189	15	138	86	95
Abnormalities/litter (%)					
External	2.9	96.9*	1.5	0.0	0.0
Visceral	17.8	100.0*	22.3	14.6	6.8
Skeletal	25.8	96.4*	31.2	14.3	19.5

* $p < 0.05$

Title: VENTILATOR SETTINGS TO MITIGATE HYPOCARBIA IN THE OBESE PATIENT

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Introduction. Many americans are obese; 1 in 5 men and 1 in 10 women are 20% overweight.[1] They confront the anesthesiologist with many problems including the choice of optimal ventilatory parameters. Using a routine ventilatory regimen[2] (10 cc/kg, at 10X/minute, for 100 cc/kg/min) in the morbidly obese patient often leads to hyperventilation and hypocarbia. The purposes of this study were to: (1) document the magnitude of hypocarbia produced by standard ventilatory settings; and (2) determine if ventilator settings based on ideal body weight decreased hypocarbia without causing hypoxia.

Methods. Ten morbidly obese patients, without lung disease and scheduled for non-thoracic surgery under general anesthesia, were studied with institutional approval after informed consent was obtained. Body mass index, the quotient of weight and height^2 [BMI = kg/m^2 (a)], was used to determine morbid obesity, which was defined as BMI > 30. Rearranging (a) to kg = BMI X m^2, we calculated lowest obese weight (LOW) and ideal body weight (IBW) from respective BMI values of 30 and 25. For example:

> A patient with a true body weight (TBW) = [139 kg., and a height of 177 cm (1.77 m)], has a BMI = 139/(1.77 m)^2 = 44.4.
>
> The corresponding LOW (weight at BMI = 30) is: 30 X (1.77 m)^2 = 94 kg.
>
> Likewise, IBW (weight at BMI = 25) is: 25 X (1.77 m)^2 = 78 kg.

All patients were premedicated with seconal (2 mg/kg IM) in doses not exceeding 200 mg. Arterial blood gases on room air were obtained prior to premedication. Monitors included an EKG, temperature probe, arterial line, neuromuscular blockade monitor, and oxygen analyzer.

Tracheal intubation followed an intravenous induction consisting of D-tubocurare (3 mg), thiopental (2-3 mg/kg), succinylcholine (1.5 mg/kg), lidocaine (100 mg), and fentanyl (1 mcg/kg). Anesthesia was maintained with 50% N_2O/O_2, and ethrane 1.5-2%. Pancuronium (50 mcg/kg) provided relaxation. Tidal volume was measured with a Wright's Respirometer and vaporizer accuracy was confirmed by gas chromatography.

All patients were sequentially ventilated (12 cc/kg X 8/min) according to TBW, LOW, and IBW. Adequacy of ventilation was determined at each setting by measuring blood gases. The statistical significance of differences in $PaCO_2$ at each setting were assessed by Student's T tests.

Results. Table 1 shows $PaCO_2$ for each patient at three ventilator settings. All ventilator settings produced $PaCO_2$s below 40 torr. However, IBW ventilation produced more normal levels. Mean $PaCO_2$ with TBW ventilation was 27.6 ± 3.2 torr, compared to 30.6 ± 4.5 torr with LOW ($p < 0.005$) and 32.8 ± 4.6 torr for IBW ($p < 0.001$). Oxygen saturation did not vary significantly within patients; values between patients varied 1.6 - .2%, mean = .79%.

Graph I depicts the correlation between $\Delta PaCO_2$ and true BMI with TBW ventilation [$\Delta PaCO_2 = -8.25 + 0.51$ BMI; r = 0.75, ($p < 0.01$)]. There was no significant correlation between $PaCO_2$ and the patient's actual weight [$\Delta PaCO_2 = -1.12 + 0.11$ TBW; r = 0.53, ($p > 0.05$)].

Discussion. Body density and skinfold thickness are widely accepted as measures of obesity. Body mass index correlates well with the above measures.[3] TBW ventilation produced severe, LOW produced less, and IBW the least hypocarbia. Hypocarbia induced by TBW ventilation correlated much better with BMI than with TBW. This indicates that BMI can be used to estimate the amount of hyperventilation that will result from standard ventilator settings.

In conclusion, IBW is easily calculated and can be used to determine ventilator settings which produce near normal $PaCO_2$ values, in the morbidly obese, without causing hypoxia.

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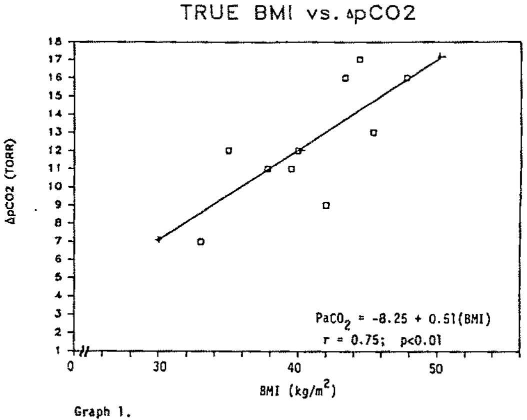
TABLE 1
PaCO2 (TORR) AT THREE VENTILATOR SETTINGS
BASED ON DIFFERENT BODY WEIGHTS *

PT.#	TBW	LOW	IBW
1	23	24	28
2	27	36	39
3	29	31	34
4	24	26	26
5	24	26	30
6	28	28	29
7	28	33	33
8	31	34	34
9	33	37	40
10	29	31	35
$\bar{X}$±SD:	27.6±3.2	30.6±4.5	32.8±4.6

*FOR DEFINITIONS SEE TEXT


TRUE BMI vs. ΔpCO2

Graph 1.
Diagram with the regression line of the correlation between $\Delta PaCO_2$(torr) and BMI(kg/m^2) at TBW ventilation.

Title: HEMODYNAMIC EFFECTS OF ATRACURIUM VERSUS VECURONIUM IN CARDIAC SURGICAL PATIENTS

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Introduction. Atracurium besylate and vecuronium bromide are two intermediate acting non-depolarizing muscle relaxants. Both of these muscle relaxants have been reported to be devoid of significant cardiovascular side-effects in man, when used within the clinical dose range.[1,2] However, other studies have indicated that atracurium may possess the potential to produce significant cardiovascular side-effects both within and above the clinical dose range.[3] This study was undertaken to determine whether or not the use of one of these muscle relaxants was advantageous over the other, with respect to hemodynamic stability, when utilizing equipotent, intubating doses of atracurium and vecuronium in cardiac surgical patients.

Methods. Ten patients scheduled for elective coronary artery bypass surgery were studied after obtaining institutionally approved informed consent. All patients received lorazepam (1-2 mg PO), morphine (0.1 mg/kg IM) and scopolamine (0.3 - 0.4 mg IM) two hours prior to the induction of anesthesia. Patients were monitored utilizing a two-lead electrocardiogram, and a central venous, pulmonary artery and radial artery catheter. Anesthesia was induced with fentanyl (150 µg IV) and lorazepam (4 mg IV). Two minutes following induction, control hemodynamic measurements were obtained and the muscle relaxant was administered as a bolus. Patients were randomly assigned to two groups in a double blind fashion. Group I patients received Atracurium - 0.5 mg/kg whereas Group II patients received Vecuronium 0.12 mg/kg. Hemodynamic measurements were then repeated at 2, 5, and 10 minutes after the drug. These included heart rate (HR), systemic blood pressure (SBP), pulmonary artery pressure (PAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). Systemic vascular resistance (SVR), pulmon- ary vascular resistance (PVR) and stroke volume (SV) were calculated from the above data. Analysis of the data was performed using Student's t-test for unpaired and paired data with significance set at $p < 0.05$.

Results. Results for Group I and Group II are shown in Tables 1 and 2 respectively. The data shows that, in the Atracurium group, systolic blood pressure fell significantly, two minutes following bolus injection of the drug; cardiac output was significantly increased 5 and 10 minutes following the drug; and systemic vascular resistance was significantly lower than control at each interval of measurement. The vecuronium group (Group II) showed no significant change in any of the hemodynamic variables measured other than a significant decrease in systolic blood pressure 10 minutes after administration of the drug.

Discussion. When caring for the patient with cardiac disease, hemodynamic stability is an integral and essential goal of any anesthetic management plan. The importance of this stability, in regard to patient outcome, has recently been emphasized.[4] In this study, equipotent doses, 2.5 times the ED_{95} for neuromuscular blockade, were utilized.[5,6] Used within this clinical dose range, vecuronium was found to produce fewer hemodynamic side effects than atracurium; particularly with respect to the lack of a significant fall in systemic vascular resistance and reflex increase in cardiac output that was seen with atracurium.

From these findings, we conclude that, within the above clinical dose range, vecuronium offers a distinct advantage over atracurium. This is particularly true when cardiovascular stability is critical in the anesthetic management of the patient with whom we are given charge.

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TABLE 1: GROUP I - ATRACURIUM (0.5 mg/kg)

	Control	2 min	5 min	10 min
HR (beats/min)	55±3.9^{+}	61.4±5.7	56.8±5.3	56.8±6.1
SBP (systolic/mmHg)	136.0±8.4	120.6±13.7*	134.8±16.1	140.8±8.8
DBP (diastolic/mmHg)	66.6±5.5	58.8±8.7	60.8±5.3	65.6±5.22
C.O. (liters/min)	3.99±0.09	4.83±.47	4.83±.37*	5.27±.50*
SVR (dynes-sec cm^{-5})	1604±130	1250±235*	1295±146*	1297±140*
PCWP (mmHg)	13.4±2.8	11.0±1.38	12.2±1.8	11.2±1.6

+ = means ± SE, n = 5 * $p < 0.05$ from control

TABLE 2: GROUP 2 - VECURONIUM (0.12 mg/kg)

	Control	2 min	5 min	10 min
HR (beats/min)	56.0±2.6^{+}	57.6±2.0	56.0±4.2	55.2±4.2
SBP (systolic/mmHg)	144.2±9.3	128.8±7.1	129.0±6.6	123.4±9.3*
DBP (diastolic/mmHg)	68.6±5.0	62.0±3.2	62.2±2.6	61.2±2.9
C.O. (liters/min)	4.75±.42	4.84±.54	4.71±.55	4.63±.63
SVR (dynes-sec cm^{-5})	1406±165	1270±131	1334±164	1349±185
PCWP (mmHg)	13.2±1.3	15.0±1.4	13.0±1.98	12.4±2.0

+ = means ± SE, n = 5 * $p < 0.05$ from control

Title: CLINICAL AND PSYCHOLOGIC EFFECTS OF FENTANYL AND NALBUPHINE IN AMBULATORY SURGICAL PATIENTS

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Introduction: Nalbuphine (Nubain^R) is an agonist-antagonist agent with an analgetic duration of approximately 3-4 hours. We hypothesized that a loading dose as the narcotic component of balanced anesthesia in day surgery (DSU) patients would confer effective analgesia throughout the recovery period. Fentanyl, on the other hand, is a short-acting narcotic which often must be given repeatedly in the postoperative period, increasing the risks of cumulation and respiratory depression. We also wanted to determine whether nalbuphine has a greater propensity than fentanyl to induce threatening psychologic side-effects in unpremedicated patients.

Methods: We compared drug dosages, length-of-stay (LOS) and incidence of psychologic side-effects of the two narcotics in a randomized, double-blinded study using unpremedicated female DSU patients having diagnostic laparoscopy. Institutional approval was obtained and informed consent furnished to all patients. They received either fentanyl, 1.5 uG/kg (F group; N = 142), low-dose nalbuphine, 300 uG/kg (LN group; N = 103), or high-dose nalbuphine, 500 uG/kg (HN group; N = 41), as initial I.V. loading-dose components of balanced anesthesia consisting of thiopental, N_2O, O_2, and a succinylcholine infusion prn. Additional I.V. intraoperative and I.M. postoperative narcotic doses, if needed, were 150 uG/kg for both nalbuphine groups and 0.75 uG/kg for the fentanyl group. All patients were given the Nowliss and Nowliss Mood-Adjective Checklist 1 - 2 days preoperatively, and again upon discharge from the DSU. Their clinical course was followed at 20 minute intervals in the recovery room (RR) and DSU by trained, blinded observers. An open-ended interview upon discharge from the DSU enabled classification and quantitation of patients' subjective reactions.

Results:

1. Dosing Frequencies: There were no significant differences in the mean number of intraoperative top-up and postoperative doses given among the LN, HN, and F groups. This indicates that the blinded anesthetists and RR nurses, despite the fact that they had control over the number and frequency of repeat dosing, nonetheless treated the 3 groups identically.

2. Postoperative Global Analgetic Efficacy Ratings: Immediately prior to discharge from the DSU, patients were asked to give a global assessment of their overall postoperative analgesia as "poor, fair, good, or excellent." These self-ratings were "good" or "excellent" in 83.6% of all the cases (N=275), with no significant differences among the 3 groups.

3. Length-of-Stay: There were no differences in duration of surgery among the 3 groups (mean = 44.8 ± 1.4 min). Time from entry into the Recovery room to removal of the I.V. was 231.2 ± 8.4 min for F, 279.7 ± 10.6 min for LN, and 276.8 ± 29 min for HN ($p<0.05$), indicating a significantly longer recovery phase for both nalbuphine groups.

4. Anxiety: There were no preoperative differences in anxiety scores among the 3 drug groups. Postoperatively, the HN group had a significantly higher score, ($p<.05$), indicating a higher degree of anxiety at time of discharge from the DSU than the other 2 groups.

5. Dreaming: The overall incidence of dreaming during anesthesia was 25% in the F group, 46% in the LN group, and 57.5% in the HN group ($p<.001$). The incidence of unpleasant dreams among those in each group who dreamed was: F = 5%; LN = 35%; HN = 39%. Thus, nalbuphine patients had significantly higher incidences both of dreaming per se during surgery and of unpleasant dreams than did fentanyl patients.

6. Drowsiness and Sluggishness: On discharge from the DSU, both the LN and HN groups had higher scores for drowsiness, sluggishness and need to concentrate to maintain alertness than did the F group ($p<.001$).

7. Satisfaction with Anesthesia: When asked what they wanted done differently next time, only 5% of all patients studied referred to aspects of their anesthesia. There were no significant differences among drug groups. No patient specifically requested that a different narcotic or different form of anesthesia be used.

Conclusion: We conclude that the regimens using both initial doses of nalbuphine clinically resemble fentanyl judging by intraoperative and postoperative dosing frequencies and the patients' self-ratings of their overall postoperative analgesia. LOS and postoperative sluggishness, however, are increased with nalbuphine, a disadvantage in the DSU. The incidences of psychologic side-effects, including dreaming per se, unpleasant dreams and postoperative anxiety, are all higher with nalbuphine and may be dose-related. However, patient acceptance of the drug was high and not significantly different from fentanyl, implying that these effects are not threatening to patients.

TITLE: ANESTHETICS AND SEDATIVES ALTER TISSUE PROTON NMR RELAXATION PROPERTIES

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Introduction

Nuclear magnetic resonance imaging (NMRI) is being used with increasing frequency to assess pathological changes in tissues. Most animal experiments and many patients will require anesthesia or sedation during such studies. The effects of these drugs on NMRI have not been previously reported. As the images are based predominately on the two water proton relaxation times T_1 and T_2, we have evaluated the in vitro proton NMR relaxation times (T_1 and T_2) of the tissues of rats anesthetized or sedated with commonly used drugs.

Methods

Twenty seven healthy unpremedicated female Sprague-Dawley rats were studied. Three animals received each drug. 1. Sedative doses of diazepam, lorazepam and flurazepam were used. 2. Intravenous anesthetics studied were pentobarbital and Innovar. In both groups, the animals were sacrificed one hour after drug administration. 3. The inhalational anesthetics used were 1.1 MAC of halothane, enflurane and isoflurane vaporized in air/oxygen. They were anesthetized for one and a half hours before sacrifice. A control group received no medication. All animals were sacrificed by cervical dislocation. The tissues were promptly dissected and handled according to published guidelines.[1] Heart, lungs, brain, liver, kidneys, spleen, muscle and uterus were examined.

The proton T_1 and T_2 values were measured on a Praxis II proton NMR (Praxis Corp, Texas) at 10.7 MHz by saturation recovery and spin echo sequences respectively. Statistical analysis comparing the treated animal with controls was performed by ANOVA with Dunnett's test and $p<0.05$ was considered significant.

Results

All statistically significant changes are indicated on the table.

Table

DRUG	ABNORMAL T_1 and/or T_2		
Innovar	Liver↑		
Pentobarbital	0		
Halothane	Muscle↑	Spleen↑	
Enflurane	Muscle↑	Spleen↑	Lung↑
Isoflurane	0		
Diazepam	Lung↓	Spleen↓	
Flurazepam	Lung↓	Spleen↓	
Lorazepam	Lung↓	Spleen↓	

0 = no change in any tissue
↑ = increased T_1 or T_2
↓ = decreased T_1 or T_2

Conclusions

1. Except pentobarbital and isoflurane, anesthetics and sedatives produce statistically significant changes in the water proton relaxation times. The effects are tissue and drug specific and must be taken into consideration in studies utilizing in vitro NMRI. Similar effects could be anticipated with in vivo NMRI but confirmation is required. 2. Changes in tissue hydration or water compartmentation are likely responsible for the changes in T_1 and T_2. The absence of a measureable effect of any of these drugs on brain relaxation times suggests that the mechanism of anesthesia is not associated with major changes in brain water distribution.

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Title: PATTERNS OF ACUTE RENAL FAILURE (ARF) REQUIRING DIALYSIS AFTER OPEN HEART SURGERY

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Introduction. Acute renal failure (ARF) after cardiac operations is usually attributed to severe peri-op cardiovascular failure or to toxic insults to the kidney (1,2). Such associations are occasionally not present. This survey was undertaken to examine, from a computerized patient registry, the characteristics and outcome of patients (pts) requiring dialysis after cardiopulmonary bypass, and to identify factors leading to ARF in these subjects.

Methods. 2468 subjects undergoing open heart surgery between Jan. - Nov. 1984 formed the study population. Only pts requiring post-op dialysis were included in the ARF category; those with lesser degrees of post-op renal dysfunction not needing dialysis, and those on dialysis before operation were excluded. Pts with baseline serum creatinine (Cr) > 1.6 mg/dl were defined as having pre-op renal dysfunction. Those requiring intra-aortic balloons, or pharmacologic hemodynamic support in the ICU for at least 7 days, were defined as having "severe hemodynamic failure".

Comparisons, by t-test or X^2 test, between pts who did and did not require dialysis were made for the following factors which may influence the development of peri-op ARF: age; pre-op Cr; angiographic LV function; hypertension; diabetes; pre-op hemodynamics; surgical, CP-bypass and aortic-crossclamp times; peri-op urine output; post-op arrest or shock; and "severe hemodynamic failure" as defined above. Statistical significance was set at $P < 0.05$.

Results. From 2468 pts, 29 (1.2%) developed ARF in the first week after operation, and were dialysed. Of these, 9 (32%) had stable peri-op hemodynamics. 48% were on dopamine during operation. Nephrotoxic drugs were not used in any patient before the onset of ARF.

48 of the 2468 pts had pre-existing renal dysfunction, of whom 10 (21%) required dialysis after operation. This was significantly higher ($P < 0.001$) than the incidence of dialysis in pts with pre-op normal kidney function (19/2428 pts; 0.8%). Comparison in this group (48 pts) between those who did and did not need dialysis showed that "severe hemodynamic failure," as defined above, was more common in those who were dialyzed (70% vs 13%, $P < 0.001$). None of the other factors identified in "Methods" differed significantly between these groups; however, hypertension and diabetes were more frequent in pts needing dialysis than in those who did not (80% vs 58%, and 30% vs 15% respectively, $P > 0.05$).

Pts with normal kidneys pre-op (n=19) and those with pre-op renal dysfunction (n=10) showed similar patterns with ARF. Cr increased, on average, 2.9 days post-op, reaching a maximum at 10.7 days. Extracorporeal renal support was started on the 6th day, and continued for a mean of 9.5 days. 83% of pts were oliguric; mortality was 61%.

8 additional pts developed late ARF after multi-organ failure. In this group, Cr increased, on average, at 18 days post-op and peaked at 30 days. The majority of these pts (63%) were non-oliguric. Dialysis was started, on average, on the 23rd day. Mortality was 75%, attributable to multi-organ failure. In these 8 pts, peri-op hemodynamic failure was of comparable severity to those who had early ARF, yet early ARF did not occur. In fact, renal function was preserved while other organs were failing.

53 pts from the registry were identified as having "severe hemodynamic failure", of which 21 (40%) received intra-aortic balloon support, and the rest need pharmacologic support for at least 7 days. 9 (17%) had multiple cardiac arrests, and in 10 (19%) the chest could not be closed at operation because of poor hemodynamics. Of these 58 pts, only 20 (38%) developed early ARF.

Discussion. The present survey done in a large population shows that, contrary to previous reports (1,2), ARF after open heart surgery occurs in the absence of severe cardiovascular failure or toxic insults to the kidney, in a surprisingly large percent of patients. Even with "severe hemodynamic failure," as defined above, only 38% developed post-op ARF, and in these pts, it was not possible to predict, by comparing factors outlined in "Methods," who would develop ARF. Further, 31% of pts who did have early ARF showed stable peri-op hemodynamics with no identifiable insults to the kidneys. A cause for ARF in these pts was not found.

The observation that the incidence of post-op ARF is 26 times higher in pts with pre-existing renal dysfunction is important, though not unexpected. In this group with pre-op renal dysfunction, an association between post-op dialysis and peri-op cardiovascular compromise was more certain: 70% of those who had peri-op "severe hemodynamic compromise" showed worsening of renal function post-op requiring dialysis.

Our overall incidence of ARF is comparable with previous reports (2). Two patterns of ARF emerged: an early type ARF which was predominantly oliguric, evolving within days of operation, and late, non-oliguric ARF occuring a few weeks after surgery as a terminal event in pts with multi-organ failure.

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Title: CHANGES IN OXYGEN SATURATION DURING ELECTIVE TRACHEAL INTUBATION IN INFANTS

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Introduction: Anatomic and physiologic considerations usually mandate tracheal intubation for anesthesia in young infants. Most authorities advocate awake intubation for neonates. In some cases there are compelling indications for this practice including concern for possible undiagnosed airway anomalies and the risk of aspiration. However, awake intubation in a vigorous struggling infant may result in soft tissue trauma, hypertension, breath-holding, laryngospasm, hypoxemia, and bradycardia. No published studies examine the changes in arterial oxygenation between intubations performed in awake (AWAKE) vs. paralyzed (PARALYZED) young infants. A noninvasive device (1) which measures continuous oxygen saturation (Nellcor Pulse Oximetyer Model N100) enabled us to monitor arterial oxygen saturation during intubation.

Methods: With the approval of our Human Subjects Committee, we studied 58 intubations performed in 38 infants under the age of 4 months undergoing elective tracheal intubation. The child's anesthesiologist selected the method of intubation without influence from the investigators. A modified laryngoscope blade-the 'Oxyscope (2)-was used to insufflate oxygen during awake intubation at the personal preference of the anesthetist. Anesthesia residents in training initially attempted all but 2 intubations. We noted the number of successful intubations on first trial (# success 1st try), the number of trials per patients (trys/pt.), the difference between the pre-intubation O_2 Saturation and the lowest saturation reached during intubation (Drop O_2Sat), and the incidence of O_2Sat below 85% which corresponds to a PaO_2 of approximately 40 mmHg if a normal hemoglobin saturation curve for a neonate is assumed.

Results

TABLE 1 - OXYGEN SATURATION DURING INTUBATION

	Group 1 AWAKE	Group 2 AWAKE	(Group 1+2) All AWAKE	Group 3 PARALYZED
# pts.	11	7	(18)	20
# trials	24	10	(34)	24
# success 1st try	5/11	5/7	10/18	17/20
trys/pt.	2.2	1.4	1.9	1.2
Drop O_2Sat median	-13	-16	-13	-4
O_2Sat 85%	13/24	7/10	20/34	3/24

When we examined the data, we found that our anesthesiologiolists were more likely to choose PARALYZED intubation in the larger and older infants. We therefore selected a subset of age and weight matched newborn infants done with AWAKE and PARALYZED techniques to examine whether this bias affected the results.

TABLE 2 - NEWBORNS ONLY-OXIMETRY DURING INTUBATION

	Group 1 AWAKE	Group 2 AWAKE	(Group 1+2) ALL AWAKE	Group 3 PARALYZED
	Oxyscope	Room air		
# pts.	9	6	(15)	9
3 trials	16	7	(23)	10
Drop O_2Sat	-13	-24	-16	-6
O_2Sat 85%	8/16	6/7	14/23	2/10

The difference observed in Drop O_2Sat between AWAKE and PARALYZED intubation remained significant (p .02, Wilcoxon's rank sum test) even in this lower age group of babies.

Complications (number of patients) included endobronchial intubation (1), esophageal intubation (1,SaO_2=29%), T-wave inversion associated with a low saturation (1,SaO_2=25%) and airway trauma with bleeding and stridor (1) in babies undergoing AWAKE intubation. One infant in the PARALYZED group with Trisomy 18 and a full stomach could not be mask ventilated between intubation attempts (SaO_2=78%). No bradycardia or laryngospasm was observed in either group.

Conclusions: In this series, tracheal intubation in the presence of anesthesia and neuromuscular blockade minimized the degree of arterial hypoxemia when elective intubation was required. Not only did oxygen saturation drop more with each AWAKE than with PARALYZED intubation, which compounded the exposure of the infant to hypoxemia. Our results may reflect a relative unfamiliarity with infant anatomy found in anesthesia residents in training. The findings may be different with more experienced laryngoscopists. Further study is needed to resolve this possibility.

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Title: COMPLETE REVERSAL OF DEEP PANCURONIUM BLOCK REQUIRES AT LEAST 20 MINUTES

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Introduction. The time to antagonize a very deep (≥90%) non-depolarizing neuromuscular blockade can be prolonged[1]. Too great a dose of anticholinesterase may potentiate rather than antagonize such a block[2]. This study determines the optimal dose and timing required for Neostigmine (Neo) and Glycopyrrolate (Gly) to reverse a very deep pancuronium-induced neuromuscular blockade.

Methods. 27 ASA I-II surgical patients ages 19 to 59 years gave informed consent. After premedication with Diazepam and Morphine, anesthesia was induced with Thiopental and maintained with N_2O (66%) and narcotics. Ventilation was controlled to maintain end tidal CO_2 of 30 to 40mmHg. Neuromuscular function was monitored by measuring evoked thumb adduction in response to supramaximal ulnar nerve stimulation of 0.2msec duration at 2HZ for 2 seconds every 10sec. After stabilization of twitch heights, Pancuronium was administered and increments given to obtain approximately 95% inhibition of T1 at the time of reversal. Antagonism was with a fixed ratio combination of Neo and Gly (1ml=Neo 1mg and Gly 0.2mg), given over 1 minute. Patients were randomly allocated to receive Neo with Gly, 30μg/Kg with 6μg/Kg (low dose), or 60μg/Kg with 12μg/Kg (medium dose), or 80μg/Kg with 16μg/Kg (high dose). Neuromuscular monitoring was continued for at least 30 minutes in 24 of 27 patients. If a T4/T1 ratio of 0.75 had not been achieved by this time patients were assessed clinically and given increments of antagonist as necessary. Results were compared by analysis of variance and student's t-test where appropriate.

Results. Data is summarized in the table. The 3 patients not monitored for 30 minutes achieved T4/T1 ratios as follows: 0.57 at 11.5 mins. (medium dose), and 0.54 at 17 mins., and 0.65 at 15 mins. (high dose).

Discussion. The results demonstrate that an extended time is required to antagonize a deep Pancuronium neuromuscular block. The higher doses of Neo, (60μg/Kg and 80μg/Kg), produce significantly faster recovery of T1 than low dose, (30 μg/Kg). Neo, 60μg/Kg, produces an equivalent degree of antagonism as rapidly as 80μg/Kg, and may represent the optimal dose to antagonize this degree of blockade.

However, adequacy of reversal is a clinical judgement requiring assessment of ventilation and muscular strength. In patients where such an assessment is not possible a T4/T1 ratio of 0.75 is a reasonable end point[3]. Although with the higher dose of Neo there was a tendency towards less fade, none of the doses consistently achieved a T4/T1 ratio of 0.75 within 30 minutes. Therefore whatever the dose of antagonist, adequate clinical recovery is prolonged, often beyond 30 minutes, when antagonism of deep block by long acting non-depolarizers, such as Pancuronium is attempted.

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	Dose Neo/Gly (μg/Kg)		
	30/6 (Low)	60/12 (Med)	80/16 (High)
n	9	9	9
% block of T1 at reversal	95.0±0.7	95.4±0.6	95.3±1.0
95% recovery of T1 (min)	n=8 22.0±0.8^{A}	15.75±2.5*	14.8±2.4**
T4/T1 at 95% recovery	n=8 0.52±0.06^{A}	0.61±0.03	0.59±0.04
T4/T1 =0.75 (min)	19.9(n=3) >30 (n=6)	18.8(n=3) >30 (n=5)	20.7(n=3) >30 (n=4)
T4/T1 at 30 min^{B}	0.45	0.61	0.64
25-75% recovery of T1 (min)	10.3±1.1	5.7±0.8**	5.6±1.1**

Recovery indices for 3 doses of Neo (Mean±SE)

A 1 patient >30 min
B T4/T1 at 30 min in patients who had not achieved T4/T1 of 0.75.
* $0.01 < p < 0.05$ compared with Neo 30μg/Kg
** $p < 0.01$

Title: EFFECT IN DOGS OF SELECTIVE BETA BLOCKADE ON POTASSIUM RELEASE AFTER SUCCINYLCHOLINE

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Introduction. It has been suggested that Beta (β) blockade in dogs prolongs and augments the increase in plasma K$^+$ after Succinylcholine (Sch)[1]. This is thought to be a β_2 effect[2]. This study used Metoprolol (β_1), and ICI 118551 (β_2) as selective β blockers to examine this hypothesis.

Methods. Mongrel dogs were anesthetized with Thiopental and Halothane in oxygen. Arterial and venous lines were placed and normocapnia and normothermia maintained. After stable anesthesia was established, 0.9% NaCl (3mls/Kg/hr) was infused. Sch (1mg/Kg) was given 30 minutes later. Arterial blood was drawn into pre-heparinized syringes, placed on ice, and analyzed for plasma K$^+$ with an ion selective electrode (Nova 1) at the following times relative to the Sch: -5 mins (duplicates), +1,+3,+5,+10,+15,+30,+60, and +90 mins. The response to Sch was noted during saline infusion (n=8), Metoprolol (n=6) 0.25mg/Kg over 10 minutes followed by 1μg/Kg/min, or ICI 118551 (n=6) 100 μg/Kg over 10 minutes. Both β blockers were started 30 mins before administration of Sch. Significance of the change in plasma K$^+$ was compared within groups, (baseline versus change with Sch), and between treatments, and control groups, with ANOVA and Bonferroni t-tests.

Results. Data is summarized in the table. There was no significant difference in the baseline (-5 minutes) values of K$^+$ between the groups. In all groups K$^+$ increased significantly by 3 minutes after Sch. and persisted for 30 minutes in controls and 60 minutes in β blocked animals. In controls the peak was at 3 minutes and in blocked dogs at 30 minutes. The time course of the change in K$^+$ was altered by both β blockers ($p<0.01$), but only at 60 minutes were single values of K$^+$ different from control. Metoprolol and ICI 118551 groups showed no difference from each other in the change of K$^+$ with time.

Discussion. Other investigators[1] have found Propanolol increases and prolongs the rise in K$^+$ after Sch[1]. Although β_2 blockade compared to β_1 selectively impairs the extrarenal uptake of K$^+$[2], we found no difference in the K$^+$ response to Sch in the Metoprolol and ICI 118551 groups. Thus we could not confirm a selective β_2 effect on K$^+$ reuptake following Sch. In the doses used, both β_1 and β_2 blockade in dogs affects the pattern of release of K$^+$ after Sch and delays the return to pre-Sch levels.

Acknowledgements. We are grateful to ICI for supply of ICI 118551.

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Mean change (±SEM) in plasma K$^+$ after Sch.

Time	Controls	Metoprolol	ICI 118551
-5*	4.02±0.88	4.25±0.16	4.31±0.13
+1	+0.41±0.05^{A}	+0.24±0.08	+0.24±0.09
+3	+0.79±0.13^{A}	+0.49±0.11^{A}	+0.49±0.10^{A}
+5	+0.77±0.10^{A}	+0.45±0.10^{A}	+0.46±0.08^{A}
+10	+0.63±0.09^{A}	+0.50±0.10^{A}	+0.48±0.08^{A}
+15	+0.70±0.11^{A}	+0.65±0.12^{A}	+0.67±0.09^{A}
+30	+0.64±0.19^{A}	+0.98±0.20^{A}	+0.82±0.08^{A}
+60	+0.07±0.14	+0.57±0.17^{A,B}	+0.48±0.07^{A,B}
+90	-0.18±0.07	+0.09±0.11	+0.08±0.05

* Baseline absolute values, mean of duplicate results
A Significantly different from baseline $p<0.01$
B Significantly different from control $p<0.01$

TITLE: HISTAMINE RELEASE DURING THE ADMINISTRATION OF ATRACURIUM AND VECURONIUM IN CHILDREN

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INTRODUCTION: Several nondepolarizing muscle relaxants have a tendency to release histamine. This is usually manifested as a rash and transient hypotension. These clinical signs and symptoms of histamine release are rarely seen in children.[1,2] This study was designed to evaluate the histamine releasing potential of equipotent large doses of atracurium and vecuronium by determining the plasma histamine levels.

METHODS: Twenty children (ASA I) 1-10 y were studied. The protocol was approved by our institutional review board and parental written consent was obtained. Premedication consisted of rectal methohexital (25 mg/kg) in children less than 7 years; older children did not receive any premedication. Anesthesia was induced by $N_2O:O_2$ and halothane via a face mask, and maintained at 1-1.5% inspired halothane concentration. The heart rate, blood pressure, EKG and temperature were monitored in all patients. Neuromuscular transmission was evaluated by recording the force of contraction of the adductor of the thumb in response to supramaximal stimulation of the ulnar nerve at 0.15 Hz.

Once the children were anesthetized, an intravenous blood sample (control) was obtained. A bolus dose of atracurium, 0.6 mg/kg, or vecuronium, 0.12 mg/kg, was randomly administered. Two and 5 mins after the relaxant was administered, blood samples were obtained. Endotracheal intubation was performed after the second (2 min) sample was drawn. The blood samples were collected in dry heparinized syringes, placed immediately on ice, cold centrifugation performed and the plasma separated and frozen. The samples were analyzed by radioenzymatic assay for histamine sensitive to 25 pg/ml.[3]

RESULTS: The results (mean±SE) of the study are summarized in Table 1.

		Atracurium 0.6 mg/kg	Vecuronium 0.12 mg/kg
Age (years)		4.6±0.9	5.4±0.9
Weight (kg)		19.9±2.6	21.1±2
Time to 100% depression of twitch (min)		1.9±0.2	2.2±0.4
Recovery of twitch to 5% of control (min)		38.6±2.7*	21.1±1.6*
Histamine level (pg/ml)			
Control	mean±SE	794±126	567±62
	range	(451-1834)	(148-832)
2 min	mean±SE	1780±956	570±105
	range	(411-10,250)	(110-1128)
5 min	mean±SE	981±255	557±91
		(465-2,755)	(185-1302)

*P<0.001

In the two groups of children studied there was no significant difference in the mean plasma histamine levels between the control plasma samples and the samples withdrawn 2 and 5 min after the administration of atracurium or vecuronium. However, in the group that received atracurium two children showed a marked change in serum histamine levels. One was a seven year old girl with normal control blood histamine levels (567 pg/ml), whose histamine levels quadrupled after atracurium. This child did not show any change in vital signs. The other was an 8 year boy who had an abnormal control histamine level, 1834 pg/ml, which increased to 10,250 pg/ml 2 min after the atracurium and decreased to his control level within 5 min. The BP of this child dropped from 80 mmHg systolic to 70 mmHg with no change in pulse rate and no rash was noted. This child had a history of mild but frequent allergic symptoms (rhinitis). At the time of surgery he had no such symptoms and was not on any medication. In the remaining 8 patients there was practically no change in plasma histamine level (control 693±60, 2 min:668±75, 5 min:606±41 pg/ml).

In the group receiving vecuronium none of the patients showed a significant increase in serum histamine levels.

DISCUSSION: In the present study vecuronium 0.12 mg/kg proved to be shorter acting than atracurium 0.6 mg/kg (Table 1). These doses are approximately equipotent.

A previous study in adults demonstrated a mean significant increase,[4] about 100%, in histamine levels upon the administration of a 0.6 mg/kg bolus dose of atracurium. In this study of children the increase in histamine concentration was not present in 8 patients. However, 2 of the 10 patients receiving atracurium demonstrated a marked increase in histamine levels without any significant changes in cardiovascular parameters or presence of rash; this is contrary to previous experiences in adults where most of the patients who showed an increase in histamine levels had cardiovascular manifestations.[5]

It seems that children have a tendency to release less histamine than adults after the administration of atracurium but some still do. Consequently if histamine release would be deleterious to children than vecuronium would be a better choice.

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Title: ARTERIAL OXYGEN DESATURATION AND EFFECT OF SUPPLEMENTAL O_2 DURING TRANSIT FROM OR TO PAR UTILIZING A PULSE OXIMETER

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Introduction. It has been well documented that arterial 02 desaturation develops in the early postoperative period and lasts for several hours if not days.[1,2] It is a common rule in most recovery rooms (PAR) to administer supplemental 02 in the immediate postoperative period because of the high incidence of hypoxia in patients in this setting.[3,4] Whether or not to use supplemental 02 when transporting patients to the PAR from the operating room (OR) is less clear since no data are available. We attempted to determine whether there is significant 02 desaturation during the transit period from the OR table to the PAR and to determine the effects of supplemental 02 given during this period.

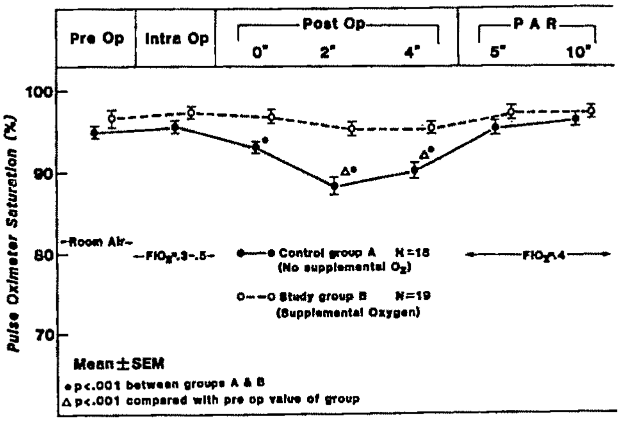
Methods. Out study proposal was approved by our institution's Human Research Committee. The patient population consisted of 37 adult patients scheduled for elective surgery lasting 45 minutes or longer. The operative procedures were varied but no upper abdominal or chest surgery were included. Patients received general anesthesia with various agents which included N20 in all but one patient. All received at least 3 minutes (mean 5 min.) of 100% oxygen breathing via a circle absorption system with a 6 l/min 02 inflow rate at the end of anesthesia prior to moving from the OR table to the transport stretcher.

We measured 02 saturation with an oximeter (Biox(R) IV) using either ear or finger probes at the following times: preoperatively after premedication while breathing room air; intraoperatively during the last 10 minutes of anesthesia; and postoperatively at 0 (after moved to stretcher), 2, and 4 minutes during transit; and 5 and 10 minutes after arrival in the PAR. The patients were randomly assigned to "control" (air breathing with no supplemental oxygen during transport) or "study" (supplemental oxygen) groups based on the last digit of the hospital number: odd-control, even-study. In the study group, supplemental oxygen delivered by a "venti-mask" at 5 l/min 02 inflow was started just before the patients were transferred from the OR table to their stretchers and continued during transport to the PAR. Upon arrival in the PAR all patients received supplemental O_2 via a "venti-mask" at flow rates of 5 l/min or more as per our usual departmental practice. Data collected included age, ASA classification, type of surgery, anesthetics used, and oxygen saturation measurements. The results were compared using Student's t-test, and linear regression where applicable. $p < 0.05$ was accepted as significant.

Results. Out of 20 "control" patients entering the study 18 finished the study with 1 eliminated for equipment malfunction and 1 because of intraoperative complications. Out of 20 patients entering the study in the supplemental O_2 group, 19 finished the study with 1 patient being eliminated for equipment malfunction. Patient age, ASA classification and preoperative value for both groups were similar (Table).

GROUP	AGE (yrs) $\bar{x} \pm$ sem	ASA I-II	ASA III-IV	PREOP SaO_2 (%) $\bar{x} \pm$ sem
Control N=18	49 ± 4.0	12	6	95.4 ± .48
Study N=19	46 ± 3.9	12	7	96.4 ± .53

In the control group (without supplemental O_2) there was a significant decrease in O_2 saturation at 2 and 4 minutes postoperatively which returned to preoperative levels when 02 was given in the PAR (Figure). In the study group there was no significant decrease in O_2 saturation. Patient age correlated significantly with desaturation (r=0.59, $p < 0.01$). Length and type of surgery, and ASA classification did not significantly affect the results.



Discussion. Our data show that in relatively healthy ASA I-II as well as ASA III-IV patients there is O_2 desaturation which is significant as early as 2 min postoperatively. Supplemental 02 during the transit period prevents this desaturation. In view of the desaturation which occurs postoperatively even in healthy patients we believe consideration should be given to routine 02 administration during transit from the OR to the PAR, especially in the elderly patient and if the transport period is not assuredly brief.

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Title: THE EFFECTS OF LOCAL ANESTHETICS ON MATERNAL AND NEONATAL PLATELET FUNCTION

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Introduction. Neonatal hemorrhagic diathesis is attributed to platelet dysfunction. Neonatal (N) platelet cell membranes do not have the same cell membrane characteristics as the maternal (M) ones do. Local anesthetics are known to inhibit platelet function. Currently, no data are available to show whether local anesthetics used in obstetrical anesthesia affect M and N platelets differently, and, if so, at what concentrations. This study assesses the effects of bupivacaine (B), lidocaine (L) and 2-chloroprocaine (2-CP) on the aggregation and α-granule release action of M and N platelets.

Methods. The protocol was approved by the local review board. Informed consent was obtained. M blood was obtained from the antecubital vein of term pregnant patients. N blood was collected from the placenta at delivery. Platelet Aggregation Studies: Sodium citrate was the anticoagulant. Platelet rich plasma (PRP) was prepared by spinning blood at 200 g for 5 min, and platelet poor plasma by spinning blood at 4000 g for 20 min. Platelet count of the PRP was 250,000±20,000 (1 SD). Adenosine diphosphate (ADP), epinephrine (Epi) or collagen (Coll) was the aggregant (Dade cluster reagents). Aggregation was performed 30 min after the addition of 1,10,100,500 or 1000 µg/ml of B,L or 2-CP. Each experiment included a saline control (n=8 for each aggregant at each concentration). Alpha granule release action occurring spontaneously in vitro was studied by measuring -thromboglobulin (β-TG) by radioimmunoassay using the Amersham kit. Circulating β-TG level was also measured in the presence of a special anticoagulant containing procaine which inhibits β-TG release after blood is collected. Drugs were dissolved in EDTA solution at the same concentrations (n=5 for each concentration). Each experiment included a control. Blood was collected in precooled tubes. All test tubes were held at 0°C for 30 min before centrifugation. Samples for circulating β-TG level measurements were centrifuged at 0°C. Control samples and samples containing local anesthetics were centrifuged at 20°C. The assay was performed on the plasma collected from the middle portion of the supernatant. In addition, venous blood from 5 nonpregnant subjects was also studied. In all samples presence of free hemoglobin was studied using a spectrophotometer. Percent inhibition was calculated for each concentration with respect to control. Results were analyzed using t test. $p<0.05$ was considered significant.

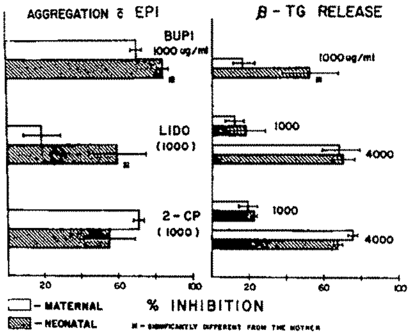
Results. Aggregation: Out of 24 N samples, only six aggregated with Epi but all N samples responded to ADP and Coll. No aggregant was affected significantly by any of the anesthetics at 1 and 10 µg/ml. At 100 ug concentration only B inhibited ADP 13±2%(1 SE) and Epi 74±5%. Coll was not affected. At 1000 µg/ml, all anesthetics inhibited all aggregants significantly. L was the least effective (Fig and Table). Of the 3 aggregants, Epi was affected the most by the 3 anesthetics. Epi was inhibited to an equal degree in M and N blood by 2-CP (Fig). However, both B and L antagonized Epi more in N blood than in M blood (Fig). All 3 anesthetics antagonized ADP and Coll more in N blood than in M blood. (Table) Release Action. The circulating β-TG levels in the M and N blood were greater than in nonpregnant controls. (nonpregnant, 54±10; M, 115±10; N, 114±10 mg/ml). None of the anesthetics affected release at 1,10 or 100 µg/ml. B inhibited β-TG release in M blood more than it did N blood at 1000 µg/ml. Both 2000 and 4000 µg concentrations of B produced hemolysis precluding β-TG assay. Both L and 2-CP produced dose-dependent inhibition at 1000, 2000 and 4000 µg/ml concentrations to an equal degree in M an N plasma (Fig). 4000 µg/ml concentration of both agents completely stopped β-TG release with values not significantly different from circulating levels.

Discussion. Both mother and fetus have increased circulating β-TG levels probably due to increased release action at the placenta. Our data show that blood concentrations of local anesthetics produced by absorption from the epidural space are unlikely to affect M and N platelet function. However, local anesthetics may attain high concentrations locally around epidural veins during regional anesthesia. High-blood levels may also result from accidental intravascular injection. Because L affects M platelet aggregation only minimally, it may be the safest agent to use especially in patients with suspected coagulation abnormality. Despite its minimal action on aggregation, L is as potent as 2-CP in inhibiting platelet release action. Thus, there appears to be a disparity between L effects on aggregation and release actions. The lack of response to Epi in many neonates has been observed by others [1] and believed to be due to lack of receptors for Epi. The increased susceptibility of N platelets may be due to their immaturity.

PERCENT INHIBITION OF PLATELET AGGREGATION(1000µg/ml)

	ADP		COLLAGEN	
	M	N	M	N
B	46.63±4.99	56.63±3.73	44.40±9	61.43± 10
L	5.00 ±1.37	10.00±2.41	13.88± 9	27.14± 12
2-CP	36.00±4.63	46.50± 2	66.86± 3	79.88±1.51

Legend: All anesthetics affect N platelet aggregation more significantly than they do maternal. Both B and 2-CP are more effective than L.



Legend: * - Significantly different from the mother. 2000 mg concentration of L and 2-CP inhibited β-TG release 30±3%, 32±5% respectively. Reference: 1. Oski FA, Nalman JL: Hematologic Problems in the Newborn. Philadelphia. WB Saunders, 1976, p 175.

Title: SUFENTANIL PHARMACOKINETICS IN BURN PATIENTS UNDERGOING SKIN-GRAFTING

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Introduction: Patients with major thermal injuries undergo complex pathophysiological changes and fluid shifts which may produce significant changes in the pharmacokinetics of drugs administered. A pilot study was designed to test whether the pharmacokinetics of sufentanil was altered in burned patients when compared to normals (1). Sufentanil pharmacokinetics have been studied in burn patients to allow a more rational use of this potentially useful narcotic.

Methods: Following Institutional Review Board approval, seven adult patients (1 female, 6 males; mean age 47 ± 15 yrs; mean body weight 68 ± 15 kg) with second and third degree burns of 42% body surface area (range 17%-60%) underwent skin grafting. The surgical procedures were performed between 12 and 85 days after the burn injury (mean 32 days). Four patients were studied on two different occasions, at least a week apart. The patients were not septic or suffering from cardiac, liver, or renal dysfunction. Mean serum albumin was 1.5 ± 0.4 g/dl (normal > 3.5 g/dl). No premedication was used. Anesthesia was induced with thiopental, 4-6 mg/kg, followed by vecuronium, 0.1 mg/kg, to facilitate tracheal intubation and maintained with 65% N_2O in O_2, mechanical ventilation being adjusted to keep end-tidal CO_2 tension between 30-35 mmHg. Ten minutes after induction 3 mcg/kg of sufentanil was given intravenously over exactly 5 min. Isoflurane was used to deepen anesthesia during surgery if heart rate and/or blood pressure increased more than 20% above preinduction levels. Ringer's lactate and packed red blood cells were transfused to maintain normal blood volume and hemodynamics. Venous blood samples were taken at 2, 5, 10, 15, 30, 45, 60 minutes and then hourly for 7 hours, and stored at -26° C until assayed. Sufentanil plasma concentrations were determined by radioimmunoassay (2). Sufentanil concentration time data for each patient were hand-fitted to a two-compartment model and the derived pharmacokinetic parameters were calculated using standard equations. Results are expressed as mean ± standard deviation.

Results: Sufentanil kinetic parameters of each patient and mean values are presented in the Table. No correlation was found between age, size of burn, postburn day, and either sufentanil plasma levels or pharmacokinetic parameters. The average duration of surgery was 160 minutes ± 77. No case of respiratory depression occurred at the end of surgery. The volume of crystalloids and the number of packed red cells units given was respectively 6.8 liters ± 2.8 and 3.9 ± 2.4.

Discussion: Sufentanil pharmacokinetics in burn patients studied at different intervals after injury are similar to the kinetics of the drug reported by Bovill et al.(1) in a relatively healthy surgical population. Mean elimination rate constant, apparent volume of distribution and plasma clearance in burn vs normal patients were respectively: 175 vs 164 min; 2.59 vs 2.66 $l \cdot kg^{-1}$; 11.15 vs 12.66 $ml \cdot kg^{-1} \cdot min^{-1}$. Replacement of large amounts of blood and crystalloid infusion did not alter the pharmacokinetics of sufentanil. Significant intraoperative bleeding, however, only occurred when sufentanil plasma levels were already low, approximately 0.9 ng/ml, with consequent small loss of drug. In addition, sufentanil clearance is mainly dependent on liver blood flow. The high plasma clearance in this study suggests that liver blood flow was adequately maintained intraoperatively. The study confirms the relatively short half-life of sufentanil. This preliminary data on sufentanil kinetics do not demonstrate any relevant difference between burned patients and the normal surgical population. Sufentanil pharmacokinetics do not seem to be markedly different in burn patients from a normal surgical population.

Table 1.
SUFENTANIL PHARMACOKINETIC PARAMETERS

Patient Number	Vc $(1 \cdot kg^{-1})$	Vd (1·kg-1)	$t_{\frac{1}{2}\beta}$ (min)	Cl $(ml \cdot kg \cdot min^{-1})$
1	1.21	3.08	219	10.67
2A	0.76	2.31	138	11.57
2B	0.66	2.13	112	13.20
3	0.53	2.03	78	18.00
4	1.08	3.38	245	9.56
5A	0.72	2.42	253	6.68
5B	0.61	2.20	172	8.86
6A	0.74	3.02	159	13.12
6B	0.64	2.18	137	10.98
7A	0.31	3.53	185	13.22
7B	0.63	2.26	229	6.84
M±S.D.	0.71±0.24	2.59±0.54	175±57	11.15±3.25

Patients 2, 5, 6, and 7 were studied on two occasions indicated as A and B.

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Title: COMPARISON OF ECG LEADS V_5, CS_5, CB_5, AND II BY COMPUTERIZED ST SEGMENT ANALYSIS

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Introduction. Monitoring of the electrocardiogram (ECG) is now routine in the diagnosis of dysrhythmias and detection of myocardial ischemia during anesthesia. Patients with a known history of ischemic heart disease (IHD) undergoing non-cardiac surgery are particularly at risk.[1] Different ECG lead systems have been recommended for the optimal detection of myocardial ischemia,[2,3] but no previous comparison of multiple leads has been made during and after anesthesia using computerized ST segment analysis.

Methods. Following approval of the institutional review committee, informed consent was obtained from 15 patients with IHD and 7 normal patients undergoing a variety of non-cardiac surgical procedures. Diagnosis of IHD was based on a clear history of myocardial infarction (MI) or ECG evidence of IHD. Patients with conduction defects or left ventricular strain pattern on the ECG were excluded. There was no restriction on age, preoperative drug therapy, type of surgery, or anesthetic management. Prior to induction of anesthesia , ECG electrodes were placed to monitor leads II, V_5 and modified chest leads CS_5 and CB_5. A modified Hewlett Packard 2008A module was used to select and display simultaneously lead II and one of the precordial leads. A Quinton 741 computerized ST segment analyser was used to detect ischemic changes in each of the leads. ST segment parameters including ST level, slope, index and integral were updated and displayed every 20 beats during induction, maintenance of anesthesia, and in the recovery room for 2-4 hours. Ischemia was defined as 1mm or more of downsloping or horizontal ST segment depression, greater than 2mm of upsloping ST segment depression measured 0.06 seconds from the J-point, or ST elevation greater than 1mm in any lead. Patients with IHD had serial 12-lead ECGs and creatine phosphokinase-myocardial bands (CPK-MB) taken postoperatively.

Results. No patients in the control group developed ECG evidence of ischemia, while 3 of 15 patients with ischemic heart disease showed ST segment changes. Two patients had ischemia in the operating room and one in the recovery room. The ST segment analysis showed ischemic changes in all leads in the 3 patients, but the changes were more easily observed in the precordial leads than in Lead II (Figure). The range of ST segment depression from control was 0.6mm in lead II to 2.2mm in lead CS_5 and was downsloping (ST slope range=-1.0 to -6.0mm/sec) in most leads in the 3 patients. The mean values for the ST segment parameters are shown in the table. Postoperative ECGs and CPK-MB measurements did not indicate ischemia/infarction in any patient studied.

Discussion. The overall incidence of myocardial ischemia (20%) was less than previously reported and no changes were found during intubation.[1] This may be related to the increased use of specific drugs (eg: nitroglycerin) to maintain cardiovascular stability during anesthesia. The episodes of myocardial ischemia were associated with hypertension in two patients and hypotension in the third case which is consistent with previous reports.[1] The ischemic changes were detected with equal frequency in all the precordial leads studied suggesting that the use of bipolar lead CS_5 or CB_5 is a satisfactory alternative to monitoring a true V_5 lead during anesthesia; especially when combined with lead II. Furthermore, use of a computerized ST segment analyzer facilitates the diagnosis of myocardial ischemia in the perioperative period.[4]

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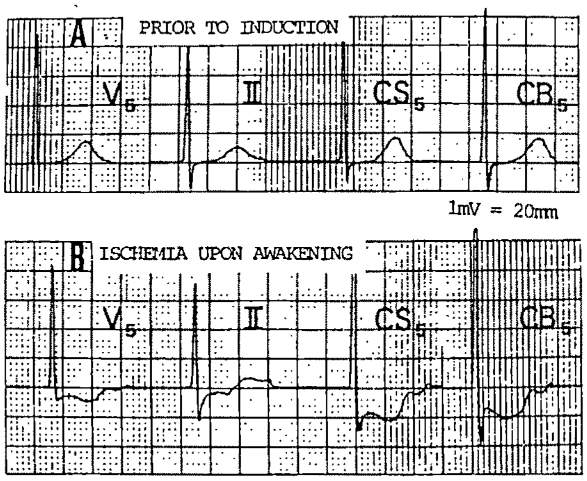

TABLE

	ECG LEAD			
	II	V_5	CS_5	CB_5
ST Depression(mm)	1.0	1.1	1.8	1.4
ST Slope (mm/sec)	-2.3	0	-2.3	-3.7
ST Index	-0.8	-0.8	-1.6	-1.7
ST Integral (μV/sec)	6.3	6.8	11.2	9.4

Title: THE EFFECT OF SLOW CHANNEL CALCIUM BLOCKERS ON PREOPERATIVE PLATELET FUNCTION

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Introduction. Coagulation abnormalities are a common problem during and after cardiac surgery. Over the last few years many new medications have been added to the regimen of the cardiac patient. Several studies have shown that some of these drugs may influence platelet function. Among these commonly seen medications are propranolol, a beta-adrenergic blocker, various vasodilators such as nitroglycerin (NTG), and most recently, slow channel calcium blockers.[1-3] Most patients are receiving at least one of these drugs on a regular basis and many may be taking combinations of two or three of these drugs. The purpose of this study was to determine if slow channel calcium blockers alone or in combination with beta-blockers and/or nitrates exert a clinically significant influence on the hemostatic mechanisms prior to the beginning of anesthesia and surgery.

Methods. After informed consent, 35 patients undergoing elective coronary artery bypass surgery were studied. Patients were divided into two groups: Group I (control) received no calcium channel blocker, while Group II received a calcium channel blocker. Both groups I and II were further subdivided as to whether patients also received beta-blockers (propranolol, metoprolol, pindolol, nadolol, atenolol, timolol) and/or nitrates. Beta-blockers, nitrates and calcium blockers were continued in their usual doses until the time of surgery with most patients receiving their last dose on the morning of surgery. Routine preoperative coagulation studies were done prior to surgery including PT, PTT and template bleeding time. All patients were premedicated with morphine and scopolamine. Standard cardiac monitoring was used including ECG lead V_5, and radial arterial and pulmonary arterial catheters, and samples were drawn from the arterial catheter for platelet count and platelet aggregation studies with ADP and epinephrine. Postoperative blood loss was documented for the first 12 hours. Statistical analysis was performed using a Student's unpaired t-test, with a significance level of $P < .05$.

Results. Patients in both groups were similar with respect to age, height, weight, and premedication. The number of patients in each subgroup on like combinations of drugs was similar. Preoperative PT, PTT, hematocrit, and template bleeding time were not significantly different and were within normal ranges. There were no significant differences between groups I and II for preinduction platelet count or ADP- and epinephrine-induced platelet aggregation (Table). Postoperative blood loss was the same for both groups. Analysis of the data using beta-blockers or nitrates as the independent variable also showed no statistical differences in any of the parameters studied.

Discussion. Many drugs used in the treatment of cardiac patients are known to have some effect on platelet function. These include beta-blockers, vasodilators and slow channel calcium blockers. The mechanism of platelet interference varies as does the degree of severity.

Propranolol has been found to inhibit platelet aggregation due to interference with intracellular calcium mobilization and reduced ability of the cells to produce Thromboxane A_2. The effects of NTG are dose-dependent and reversible by the discontinuance of the drug, but the mechanism of its action is not yet fully understood.

Verapamil, nifedipine and diltiazem have all been found to reduce platelet aggregation. Verapamil inhibits epinephrine-induced aggregation while nifedipine and diltiazem have been shown to reduce both ADP- and collagen-induced aggregation.[1-3] Nifedipine has also been shown to increase Ivy bleeding time by 12% in vivo.[2]

This study indicates that the use of slow channel calcium blockers alone or in combination with beta-blockers and/or nitrates does not produce clinically significant alterations in the normal coagulation process or in platelet function. These results suggest that patients may be safely maintained on their usual doses of calcium channel blockers until the time of surgery without concern for significant coagulopathy.

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TABLE

(X±SD)

PARAMETER	CONTROL GROUP	CALCIUM BLOCKER GROUP
Bleeding Time (min)	6.94± 1.42	8.63± 2.03
M ADP for Agg	3.5 ± 4.64	4.65±10.51
%ADP Agg	77.75± 8.93	75.81± 8.40
M Epi for Agg	7.45±16.71	8.37±23.60
% Epi Agg	75.17± 8.46	78.13± 8.20
Platelet count	178,250±31,090	196,950±77,660

Title: HEMODYNAMIC EFFECTS OF N_2O IN INFANTS

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Introduction. Although nitrous oxide is widely used in pediatric anesthesia, its hemodynamic effects have not been documented in small children. While some studies of adults have shown an increase in pulmonary vascular resistance index, index,[1,2] the response of the more muscular and and reactive immature pulmonary vasculature to nitrous oxide has not been studied. Safe use of nitrous oxide in infants with intracardiac shunting or pulmonary hypertension is debated. Our study was designed to assess the hemodynamic response of infants to 50% nitrous oxide.

Methods. We studied infants under one year of age when they were responsive but still fully ventilated 4-6 hours after surgical repair of complex congenital heart disease during high dose fentanyl anesthesia. Hemodynamics were measured using left and right atrial catheters, radial and pulmonary arterial (PA) catheters for pressures and a PA thermistor for thermodilution cardiac output. Four sequential sets of measurements were made during uniform ventilation after 12 minutes of equilibration with the gas mixtures delivered through the respirator: 50% oxygen/nitrogen (1), 50% oxygen/nitrous oxide (2), 50% oxygen/nitrogen (3), and 50% oxygen/nitrous oxide (4). FiO_2 was thus 0.5 during all measurements. Mean hemodynamic values after equilibration with nitrous oxide were compared to the preceding baseline during 50% nitrogen administration using the analysis of variance test; a p value of $< .05$ was considered significant. Institutional clinical investigation committee approval and informed parental consent were obtained for all studies.

Results. The mean hemodynamic values at the end of each measurement period are shown in the Table. Cardiac index (CI), heart rate (HR), and mean arterial pressure (MAP) all fell significantly with nitrous oxide on both administrations. Mean pulmonary arterial pressure (MPAP), left atrial pressure (LAP), right atrial pressure (RAP), pulmonary vascular resistance index (PVRI), and systemic vascular resistance index (SVRI) showed no significant change with nitrous oxide after either administration. Results were thus readily reproducible.

Discussion. We concluded from our study that 50% nitrous oxide decreases MAP in infants secondary to a decline in CI, attributable in turn to decreases in HR, similar to previous findings in adults.[1-3] Unlike the studies of adults,[1-2] the infants in this study showed no change in PVRI, SVRI, or MPAP with nitrous oxide. There was a slight tendency for PVRI to rise but this did not achieve significance. The mean PVRI was mildly elevated (> 3 wood units); 5 patients had elevated PVRI (> 3 wood units), while 4 had normal PVRI (1-2 wood units), but when these 2 sets of patients were analyzed separately neither the group with normal nor the one with elevated PVRI showed any statistically significant increase in PVRI. This suggests that even in small children with a mild degree of pulmonary vascular obstructive disease, N_2O does not adversely affect PVRI.

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Mean Hemodynamic Values with 50% Nitrous Oxide in Infants (± SD)

	(1)-N_2	(2)-N_2O	(3)-N_2	(4)-N_2O
HR (b/min)	120±20	105±13*	112±11	103±13*
MAP (mmHg)	79±6	70±6 *	80±6	72±8*
RAP (mmHg)	9±2	9±1	10±3	9±3
MPAP (mmHg)	21±5	20±5	23±6	20±6
LAP (mmHg)	10±3	10±3	11±4	10±3
CI ($L.min^{-1}.m^2$)	3.6±1.1	3.1±0.9*	3.4±1.0	3.1±0.9*
PVRI (Wood U.)	3.1±2.1	3.5±2.4	3.3±2.3	3.3±2.2*
SVRI (Wood U.)	21±5	22±5	23±6	22±5

FiO_2 0.5 at all times *$P < 0.05$

Title: SELF TAMING DOSES OF PROTAMINE PREVENT SUBSEQUENT PROTAMINE HYPOTENSION

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Introduction: There is evidence in both man[1] and dog[2] that protamine induced hypotension may be associated with changes of platelet function. The influence of white cells and complement on protamine hypotension is unclear. Animal experiments suggest that protamine administration prior to heparinization can effectively prevent protamine induced hypotension.[2] The effect of administering .75 mg/kg protamine prior to heparinization was investigated on subsequent hemodynamic changes during protamine reversal. We have measured platelet count (PLT), whole blood count (WBC), total hemolytic complement (CH_{50}), and Beta thromboglobin (BTC) prior to and following protamine reversal.

Methods: The investigation was approved by the institutional review committee and informed consent was obtained from each patient, 17 patients undergoing aortic reconstructive surgery were randomly divided into two groups. Group I (N=9) received protamine sulfate .75 mg/kg (Eli Lilly) over 3 minutes, administered 5 minutes prior to heparinization. Group II (N=8) received an equal volume of normal saline over 3 minutes. Heparin 1.5 mg/kg (porcine) was administered and ACT followed throughout the operation. Additional heparin was administered to maintain ACT less than 250 sec. After 5 minutes of stabilization of hemodynamics following aortic repair, protamine 1.5 mg/kg was administered over 3 minutes. Hemodynamic measurement included: strip chart recording of arterial blood pressure, pulmonary artery pressure, central venous pressure and HR. Thermodilution cardiac output and PCWP were obtained prior to and 2 minutes following pretreatment (N.S. or protamine) and heparinization, and again prior to reversal and 1, 3, and 10 minutes following reversal. CH_{50}, PLT and WBC were measured at these times. Blood for BTG analysis was drawn prior to reversal and 1, 3, and 10 minutes following reversal.

Results: The maximum drop in systolic and diastolic blood pressure is shown in Table 1. The mean decrease in systolic blood pressure was 8 torr in the pretreated group compared to 25 torr in the normal saline group. Similarly the maximum mean decrease in diastolic blood pressure is less in the pretreated group than in the control group. We see in Table 1 that PA diastolic pressure falls more in the normal saline group than in the protamine pretreated patients. There is significant correlation between the fall in systolic and diastolic blood pressures with the fall in PA diastolic blood pressure. There were no group differences in change in platelet count, WBC, BTG or CH_{50} following protamine reversal. Closer examination of protamine pretreated patients revealed a significant inverse correlation ($p < .05$) between platelet count decrease with pretreatment and subsequent decrease in blood pressure.

Discussion: Decreases in blood pressure occur following rapid protamine treatment in aortic reconstructive operations. The maximum decrease in blood pressure occurs 1–5 minutes following protamine administration. This decrease in blood pressure is associated with decreases in CVP and PAD pressure. These hemodynamic changes were reduced by the administration of .75 mg/kg protamine prior to heparinization. Protamine decreased platelet counts and increased circulating BTG when given to antagonize heparin. The decrease in blood pressure following heparin reversal by protamine was inversely correlated with the decrease in platelet count seen during protamine pretreatment. These data suggest that protamine administered prior to heparin alters subsequent heparin-protamine interactions. We have demonstrated decreases in blood pressure with rapid protamine reversal associated primarily with reduced preload. These hemodynamic effects were blocked by prior protamine administration. We have seen reduced platelet counts with protamine reversal and an association between platelet drop with pretreatment and subsequent hemodynamics on reversal. Data obtained from patients following cardiopulmonary bypass can not be extrapolated to patients undergoing aortic surgery possibly because of different platelet populations.

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TABLE 1

	Group I (Protamine Pretreated)	Group II (Normal Saline)
Maximum Decrease in Systolic Blood Pressure	−8 ± 8 (range 0–20)	−25 ± 22* (range 0–70)
Maximum Decrease in Diastolic Blood Pressure	−3 ± 3 (range 0–5)	−13 ± 12* (range 0–40)
Maximum Decrease in Pulmonary Artery Diastolic Blood Pressure	−1 ± 3	−3 ± 3*

All Values in mmHg ± S.D.
*P < .05 Student t test

Regression	SBP vs. PAD	R = .72	P < .005
	DBP vs. PAD	R = .8	P < .001

Title: MYOGLOBINEMIA AFTER SUCCINYLCHOLINE IN CHILDREN UNDERGOING ISOFLURANE ANESTHESIA

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Introduction: The objective of this study was to determine the incidence of myoglobinemia following the administration of succinylcholine to infants and children undergoing isoflurane anesthesia. Previous investigations by the authors showed above normal increases in serum myoglobin concentration in children undergoing halothane and non-halothane (N_20-0_2-non-depolarizing muscle relaxant-narcotic) anesthesia with significantly greater myoglobinemia in the halothane group. We sought to determine whether isoflurane, a halogenated ether, behaves as the halogenated hydrocarbon, halothane, or as a non-halogen anesthetic in its association with the occurrence of myoglobinemia following the administration of succinylcholine.

Methods: Informed consent was obtained for 18 P.S. 1 children (ages 14 months-15 years) undergoing peripheral, non-muscle dissecting surgery. Approval for blood collection was granted by the Committee on Human Research. Following induction of anesthesia with N_20-0_2-isoflurane, a pre-succinylcholine blood sample was drawn. Succinylcholine 2 mg/kg was given IV. Fifteen and sixty minutes after succinylcholine administration, blood samples were collected in serum separator Microtainers® which were centrifuged and frozen until analysis. Myoglobin RIA Kit® (Nuclear Medical Systems, Inc.) employing I-125 myoglobin was used for analysis. Each patient served as his own control. Children were observed for the occurrence of fasciculations. The isoflurane group was compared statistically with the previously studied halothane (n=18) and N_20-0_2-non-depolarizing muscle relaxant-narcotic (n=15) groups using ANOVA and the Kruskal-Wallis critical difference test.

Results: Following succinylcholine administration, a rise in serum myoglobin concentration was observed in all but one patient. There was a wide range of elevation of serum myoglobin concentration. Myoglobin concentrations at 60 minutes tended to be higher than those at 15 minutes, but did not differ significantly. Presence or absence of fasciculations had no effect on the degree of myoglobinemia attained.

SERUM MYOGLOBIN CONCENTRATION (ng/ml)

Succinylcholine 2 mg/kg

	Halothane	Isoflurane	Other
15 minutes after Succinylcholine			
Median	830	280	155
Range	61-4600	137-1075	30-520
n	18	18	15
60 minutes after Succinylcholine			
Median	1820	430	205
Range	65-7000	84-1800	30-585
n	18	18	15

Fifteen minutes following succinylcholine administration, myoglobin concentrations in all three groups differed significantly. Sixty minutes after succinylcholine administration, myoglobin concentrations in the isoflurane group differed significantly from only the halothane group. Patients receiving halothane and succinylcholine had significantly greater increases in serum myoglobin concentration than those not receiving halothane.

Discussion: Isoflurane in its association with myoglobin release from muscle following succinylcholine administration, is significantly different from halothane in its association with myoglobinemia following succinylcholine. The mechanism for increased myoglobinemia in association with the halogenated hydrocarbon, halothane, remains to be determined.

Title:

HEMODYNAMIC EFFECTS OF CONTINUOUS INFUSION OF ESMOLOL DURING CARDIAC OPERATION

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Introduction: Esmolol is an intravenous cardioselective beta-adrenergic blocking agent with rapid onset and short duration of action. Esmolol infusion has been shown to attenuate heart rate (HR) and blood pressure (BP) increases with laryngoscopy and tracheal intubation in patients with coronary artery disease (1). The present investigation in a similar group of patients was designed to evaluate the effectiveness of continuing infusion of esmolol in order to attenuate the hemodynamic responses to chest incision, sternotomy, and aortic dissection.

Methods: Twenty-one patients scheduled for coronary revascularization (CABG) gave informed consent to participate in a randomized double-blind study approved by the Institutional Review Board. Criteria for patient selection included an ejection fraction ≥ 0.40 and a left ventricular end-diastolic pressure ≤ 18 mmHg. Any patient receiving beta-adrenergic or calcium entry blocking agents had these discontinued at midnight of the day prior to operation. Premedication was diazepam (0.15 mg/kg po), morphine sulphate (0.1 mg/kg im), and scopolamine (0.3-0.4 mg/kg im) given 90 min prior to induction. HR, BP and EKG (V5) were recorded in the operating room with the patients awake until stable baseline values were obtained. Either placebo or esmolol was then infused at 500 mcg/kg/min for 2 min, followed by 200 mcg/kg/min continued until aortic cannulation. Five min after infusion was begun anesthesia was induced with diazepam (0.5 mg/kg iv), pancuronium (0.1 mg/kg iv) and 50% N_2O in oxygen. Intubation began 5 min after induction. After intubation anesthesia was maintained with 50% N_2O in oxygen and enflurane (0-2.0%) until cardiopulmonary bypass (CPB). Enflurane concentration was adjusted and adjuvant agents used as necessary to maintain HR 45-110 beats/min, systolic BP within 25% of preoperative pressure, and left atrial pressure (LAP) ≤ 15 mmHg. HR, BP, EKG (V5), and inspired enflurane concentration were recorded and analyzed at 7 stages (Table). Blood was drawn 10 hrs after aortic cross-clamp placement for determination of CK-MB.

Results: Patients given placebo (group 1) had significantly higher heart rates than patients given esmolol (group 2) at all events except sternotomy when the difference just failed to achieve statistical significance ($p = 0.06$). Mean arterial pressure (MAP) was significantly greater at intubation in patients given placebo than in patients given esmolol. At this time, two placebo but no esmolol patients developed ST segment changes consistent with myocardial ischemia. Patients not receiving esmolol required significantly more enflurane to blunt hemodynamic responses to incision and one required intravenous propranolol to treat a sustained increase in heart rate. The use of other cardiovascular agents did not differ statistically between the two groups. However, LAP was significantly higher in the esmolol than in the placebo patients (11.5 ± 2.0 vs 5.3 ± 1.1 mmHg) and two patients receiving esmolol were given nitroglycerin. Difficulty in weaning from CPB did not differ between the two groups. Postoperatively no patient had enzymatic evidence of myocardial necrosis.

Discussion: This study corroborates and extends our earlier results demonstrating that esmolol can effectively blunt hemodynamic responses to intraoperative stimuli, particularly increases in heart rate. It has recently been shown that tachycardia is related to development of ischemia intraoperatively and that this is associated with an increased incidence of perioperative myocardial infarction (2). This suggests a protective role for beta blockade in patients undergoing CABG. Esmolol offers advantages over currently available beta blockers in that its rapid onset and short duration allow more precise titration or withdrawal in response to the clinical situation. However, as with any beta blocker, careful attention should be paid to left ventricular filling pressures when esmolol is used with a potent inhalation agent.

References:

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TABLE

HEMODYNAMIC DATA

	HR	MAP	RPP	Inspired Enflurane (%)
Stage I	BASELINE			
Group 1	73±3.9	92±3.5	10624±814	
Group 2	68±2.5	90±4.2	10249±711	
Stage II	PRE-INDUCTION			
Group 1	73±4.1	92±4.1	11020±994	
Group 2	63±2.4*	88±5.1	9177±819	
Stage III	INDUCTION			
Group 1	92±4.4	81±4.2	12593±1047	
Group 2	79±2.7*	74±6.2	9602±863*	
Stage IV	INTUBATION			
Group 1	94±5.5	122±4.8	15779±1543	0.83±.18
Group 2	77±2.6*	104±4.1*	12098±719*	0.18±.09*
Stage V	CHEST INCISION			
Group 1	85±5.9	107±6.1	12965±1278	1.70±.21
Group 2	68±3.2*	104±5.1	10064±497*	1.14±.13*
Stage VI	STERNOTOMY			
Group 1	78±5.6	101±6.6	11259±1381	1.77±.20
Group 2	66±3.1	95±5.1	8924±610	1.35±.16
Stage VII	AORTIC DISSECTION			
Group 1	79±4.9	92±5.4	10546±1240	1.27±.22
Group 2	66±3.6*	97±4.5	8882±582	1.10±.17

Mean ± SEM. * $p < 0.05$ esmolol vs placebo.

Study supported by American Critical Care (grant #8052-83-27-01).

Title: HALOTHANE PRODUCES DOSE-DEPENDENT MYOCARDIAL DEPRESSION IN MAN DURING FENTANYL ANESTHESIA

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Introduction The end-systolic pressure-dimension relation has been used to study the effects of volatile anesthetics on ventricular function in man (1,2) and in dogs (3). Although the effect of halothane at a single end-tidal concentration is known, no dose-response studies exist in man. Using a 2D-echo method to derive the end-systolic pressure-volume relation (ESPVR) in the anesthetized patient, this study investigated the dose-dependence of the effect of halothane on myocardial function in man and the sensitivity of the ESPVR to detect myocardial depression.

Methods Informed consent was obtained from patients scheduled to undergo coronary bypass surgery. In all patients anesthesia was induced with fentanyl, pancuronium, and 100 % O_2, and maintained with fentanyl (total dose: 100±15 mcg/kg). The ESPVR measurements were obtained immediately before or after cardiopulmonary bypass (CPB). Continuous recordings of the radial artery pressure and of the left-ventricular short-axis area, obtained by epicardial placement of a 3.5 mHz ATL® transducer, were synchronized. During the recording, 200-500cc of pump-fluid were rapidly transfused into the right atrium. The recordings were then interrupted and halothane was administered until a stable end-tidal concentration was achieved. A repeat transfusion was then performed while pressure and 2D-echo data were again recorded. With the information from each transfusion, an ESPVR-slope was constructed using >6 separate cardiac cycles. Peak-systolic pressure was defined as end-systolic pressure, while end-systolic volume index was derived from the smallest short-axis area for the studied heartbeat. All echo-data were analyzed by a "blinded" investigator using a Diasonics® interactive computer.

Results ESPVR slopes derived in 2 patients before CPB and in 3 patients after CPB were averaged at several halothane concentrations. Control left ventricular contractility at zero end-tidal halothane was represented by a mean ESPVR slope of 0.27±0.04 mmHg/ml/m^2 (±SE). At an average end-tidal halothane concentration of 0.76%±0.04% (±SE) the mean ESPVR slope decreased to 87%±10% (±SE) of control. At 1.17%±0.03% (±SE) end-tidal halothane, there was a further decrease to 71%±24% (±SE) and at 1.61%±0.1% end-tidal halothane, the mean ESPVR slope was 54%±9% (±SE) of control. These results are summarized in the figure.

Discussion Our results show that halothane decreases ventricular contractility in man under fentanyl-pancuronium anesthesia in a dose-dependent fashion. The only other human study using pressure-diameter analysis showed a 30% decrease in myocardial performance at 0.5% end-tidal halothane (1). In dogs, the dose-dependent effects of halothane were investigated by means of the end-systolic pressure-diameter relation using chronically implanted ultrasonic microcrystals to obtain ventricular dimensions (3). That study showed a 60% reduction in the end-systolic pressure dimension slope at 2% end-tidal halothane concentration. The ESPVR derived in this study using 2D-echo appears to be an equally sensitive index of ventricular contractility in man. It provides the first intraoperative evidence that halothane myocardial depression is dose-dependent.

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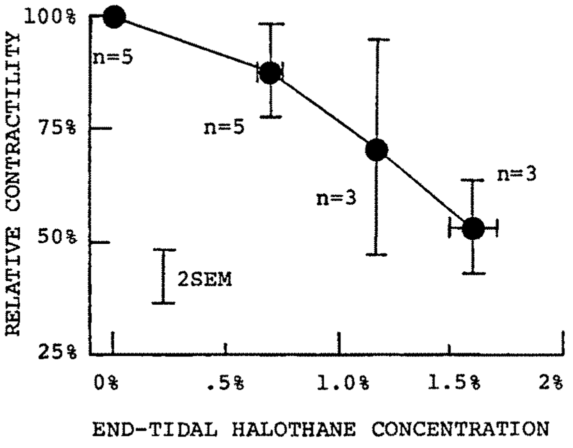

Title: A NEW METHOD FOR THE INTRAOPERATIVE DETERMINATION OF CONTRACTILITY
Authors: Z Hillel, M.D., D Thys, M.D., BP Mindich, M.D., ME Goldman, M.D., JA Kaplan, M.D.
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Introduction In animals and isolated animal hearts, the end-systolic pressure-volume relation (ESPVR) has recently been introduced as an index of ventricular contractility (1). The ESPVR is obtained from the linear relation between end-systolic pressure (ESP) and end-systolic volume (ESV). The slope of this relation is called elastance (E) and is proportional to contractility. The present study first determined whether intraoperative left ventricular (LV) ESPVRs could be constructed for patients. Second, the hypothesis that agents with known inotropic properties alter the ESPVR in the anticipated directions was tested.

Methods After institutional approval and informed consent had been obtained, 34 patients scheduled for CABG were administered fentanyl-pancuronium anesthesia with 100% O_2. The radial artery pressure tracing and a 2D epicardial echocardiogram (3.5 mHz ATL® transducer) were recorded simultaneously after synchronization. To produce an increase in arterial pressure, 200 to 800 cc of oxygenator contents were rapidly transfused into the right atrium using a cannula connected to the CPB pump. To maintain constant heart rate, patients were paced atrially. Respiratory interference was avoided by interruption of mechanical ventilation during the measurement period which never exceeded 60 seconds. The peak arterial pressure of individual beats was used to estimate ESP. Endocardial short-axis areas at the mid-papillary muscle level were computed using a Diasonics® computer-interfaced electronic pen digitizer. For each contraction, the smallest short-axis area (SA) was used to calculate ESV according to the formula $ESV=(SA)^{3/2}(45+SA)/(15+SA)$ and ESVI=ESV/BSA. All tracings were performed by a "blinded" investigator in triplicate. For each transfusion, the E slope was derived by best-fit linear regression using the relation ESP=E x ESVI + constant. Four to 12 pairs of ESP-ESVI data were used in the determination of each slope. Sensitivity and specificity of ESPVR to changes in ventricular contractility were determined by repeat measurement of the slope after administration of dopamine (5 mcg/kg/min) to increase E, or halothane (1% end-tidal) to decrease E.

Results Baseline elastance slopes derived in 34 patients ranged from 0.17 to 4.85 with a mean of 1.22 ± 0.9 mmHg/ml/m^2 ($\pm$SD). The correlation coefficients for the linear fit of the ESPVR averaged 0.93 ± 0.04 ($\pm$SD) indicating very good linearity between ESP and ESV. Sample ESPVR slopes are shown in the figure. Echo analyses repeated at different times by the same investigator showed good reproducibility of E. Dopamine infusion produced steeper ESPVR in 11 out of 11 transfusions, while halothane administration made the ESPVR less steep in 10 out of 12 transfusions. These interventions indicate that the ESPVR slope obtained intraoperatively was 100% sensitive to changes in the inotropic state of the LV with an 83% specificity (Table 1).

Discussion A new intraoperative method is described which allows the measurement of LV contractility from the ESPVR. The ESPVR was obtained by increasing LV preload gradually in a short period of time. The ESPVR showed very good linearity when subjected to regression analysis. Changes in the slope of the ESPVR reflected changes in the contractile state of the LV produced by dopamine or halothane with good sensitivity and specificity. Thus the slope of the ESPVR in patients appears to faithfully represent intraoperative LV contractility. The non-dependence of the ESPVR on ventricular loading factors as demonstrated in the dog model needs to be confirmed in man. This will make the ESPVR an excellent method to investigate the effects of new anesthetic agents on ventricular contractility.

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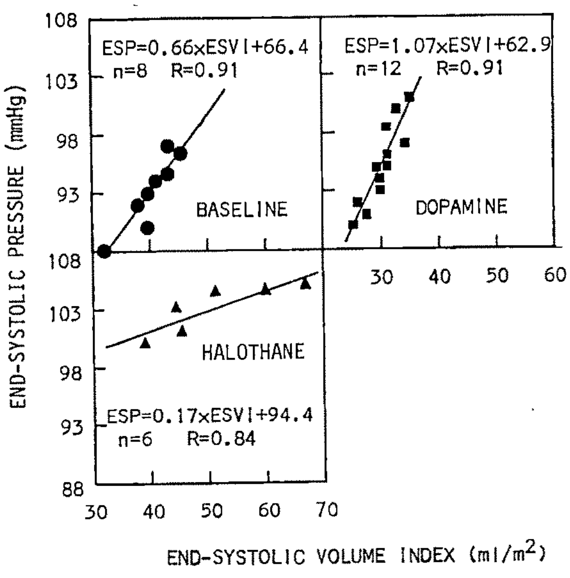
TABLE 1

	Increased E	Decreased E
Dopamine	11 (TP)	0 (FN)
Halothane	2 (FP)	10 (TN)

TP=True positive	FP=False positive
TN=True negative	FN=False negative

SENSITIVITY = 100x TP/(TP+FN)
SPECIFICITY = 100x TN/(TN+FP)



Title: **MUSCLE RELAXANT - BETA BLOCKER INTERACTIONS DURING HIGH DOSE NARCOTIC INDUCTION**

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Introduction. High dose narcotic induction for cardiac anesthesia can cause severe bradycardia especially in patients (pts) who are well Beta (B) blocked. Pancuronium (P) is often utilized to counteract this bradycardia and provide stable hemodynamics. However, with the advent of calcium channel blockers, pts are taking less B-blockers to achieve an optimal myocardial oxygen balance. In this subset, administration of a muscle relaxant with less sympathomimetic action seems appropriate. We evaluated the use of metubine-pancuronium (M/P) and vecuronium (V) in incompletely B-blocked pts during sufentanil (S) or fentanyl (F) induction. Pancuronium (P) was evaluated in well B-blocked pts during S or F induction.

Methods. With informed consent and institutional approval 65 pts. undergoing 3 vessel bypass or aortic valve replacement were analyzed. Cardiac medications were continued up to the time of surgery. All pts were premedicated with lorazepam (0.04 mg) and morphine (0.1 mg/kg). 10 ml/kg of Ringer's lactate was infused prior to induction as the arterial and Swan-Ganz catheters were inserted. Clinically B-blocked pts received P 0.1 mg/kg whereas incompletely B-blocked pts received either M/P 0.15 mg/kg and 0.05 mg/kg respectively or V 0.1 mg/kg. Induction was achieved with F 50 ug/kg or S 10 ug/kg and muscle relaxants while ventilation was maintained with 100% O_2. Hemodynamics, induction, and intubation times were recorded continuously. For statistical evaluation the analysis of variance and a modified t-test were used. Differences were considered significant at the 0.05 level.

Results. The group on the lowest doses of B-blocker was the M/P treated pts whereas the P treated group had the highest dose of B-blocker as shown in Fig 1. With respect to heart rate (HR) the F-P group had a 5% increase in HR whereas the S-P group had a 4.5% reduction in HR as shown in Fig 2. The narcotic-M/P groups had a transient 4% rise in HR. With V, both narcotic groups decreased their HR by approximately 10%. Both the F and S treated pts maintained their blood pressure and cardiac output within 10% of their pre-induction levels. Decreases were found more commonly in the groups recording the greatest drop in HR. No signs of ischemia or failure were detected by ECG or a change in pulmonary capillary wedge pressure.

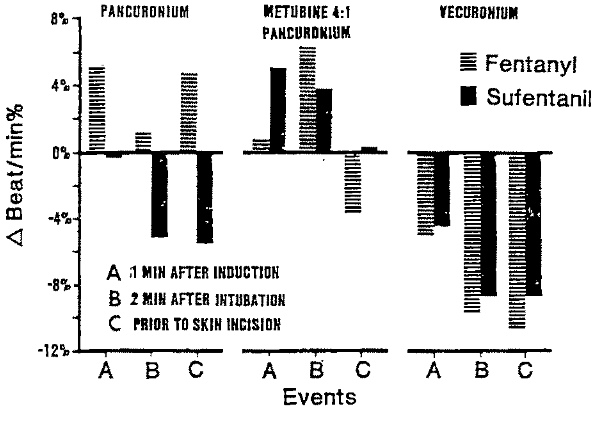
Discussion. We did not find the significant HR changes with S-P found in Khoury et al's study. Their pts received greater doses of P (0.12 mg/kg vs 0.1 mg/kg) and may not have been clinically B-blocked. In addition, we administered the S and P simultaneously. Our F-P group, however, had a 5% increase in HR. The narcotic-M/P groups had a transient 4% increase indicating that the 0.5 mg/kg still had a vagolytic effect when the pt was not well B-blocked. The narcotic-V combination caused a predictably consistent fall in HR indicating that V had no vagolytic effect on HR. However, the lowest HR recorded was 58 and no treatment was necessary. We did not find that S had less of a vagal effect than F since similar decreases in HR occured in the S-V or F-V groups and the S-P group actually had a reduction in HR whereas the F-P group had an increase in HR. Thus, V doesn't counteract the chronotropic effects of the narcotics as do M/P and P. Concomitant use of muscle relaxants and narcotics produce predictable changes that are not always desirable, depending on the pt's physiologic status and preoperative medication. In pts who are fully B-blocked caution should be used in the use of V as either F or S can produce bradycardia. However in pts on moderate doses of B-blockers, V used with either F or S results in a stable BP and a small (approximately 10%) decrease in HR, the ideal result for pts with coronary artery disease. We conclude that the lack of significant cardiovascular effects with V can be used to advantage in narcotic induction for cardiac pts, though caution should be exercised in fully B-blocked pts where P or M/P still has a place.

FIG. 1 CONCURRENT MEDICATIONS

Narcotic Group			Relaxant Group pancuronium	metubine-pancuronium	vecuronium
fent	propranolol	mg/day	176.67 ± 82.61	31.43 ± 14.60	50.00 ± 34.64
	nifedipine	"	-	20.00 ± 17.32	33.00 ± 5.77
sufent	propranolol	"	175.63 ± 97.71	38.13 ± 16.08	93.30 ± 58.5
	nifedipine	"	-	12.50 ± 5.00	30.00 ± 00

FIG. 2

PERCENT CHANGE FROM PRE-INDUCTION HEAT RATE



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Title: ISOFLURANE (I) CHANGES THE CARDIAC AND REGIONAL EFFECTS OF THE CALCIUM CHANNEL BLOCKER (CB) NICARDIPINE (Nc) IN DOGS.

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Introduction. There have been no studies published on the interaction between a dihydropyridine (DHP), CB, and I. In a chronically instrumented dog model, we have studied the effect of several doses of Nc, a DHP-CB, awake (A) and during 1.6% (L) and 3.0% (H) I anesthesia.

Methods. Nine conditioned dogs were instrumented for measurements of aortic (A), left atrial (LA), and left ventricular (LV) pressures (P), cardiac output (CO), coronary (Cor), and renal (Ren), blood flows (BF). Nc was injected as a bolus of 5, 10, 50 (n=6), and 30 ug/kg (n=9) intravenously to conscious dogs on separate days. During L-I anesthesia, 30 ug/kg (n=9) was studied one day, and 5, 10 and 50 ug/kg (n=6) were studied on another day. The effects of all Nc doses (n=6) were studied during H-I on a separate day. All doses were given in randomized order. I anesthesia was induced by mask. The dogs were intubated and ventilated with a mixture of $I:N_2:O_2$ to maintain paO_2 and $paCO_2$ at awake levels. Arterial blood samples were collected before and 1 minute after injection of Nc (30 ug/kg) awake and during L-I. Plasma Nc concentrations were measured by gas-chromatography. Statistical analysis employed a repeated measure ANOVA and paired t-tests with a Bonferroni correction. All results were given as mean ± SEM.

Results. The hemodynamic effects of Nc, awake and during L-I and H-I are presented in figure 1. The hemodynamic effects of I were essentially the same as those seen in previous studies[1]. In awake dogs, Nc induced a dose-dependent increase in heart rate HR, CO and CorBF and LV dP/dt max and a dose-dependent decrease in MAP. RenBF remained essentially unchanged. During L-I, although the Nc induced decrease in MAP was similar, Nc induced increases in HR, CO and CorBF were less, and LV dP/dt max and RenBF decreased. Except for the decrease in MAP, H-I accentuated the changes produced by L-I on the effects of Nc. Nc plasma concentrations were higher during I than awake.

Discussion. I produced a dose related blunting of the hemodynamic effects of Nc although MAP was decreased to a similar degree. Increases in HR, CO and LV dP/dt max were either blocked (HR, CO) or decreased (LV dP/dt max) by increasing doses of I. The increase in CorBF was reduced and RenBF was decreased by Nc during I anesthesia. These effects may be related to inhibition of the baro-reflex by I[2]. This hypothesis is supported by the observation that the same effect can be recorded after ganglionic blockade in conscious dogs[3]. Nc has a major advantage over the commonly used DHP-CB nifedipine. It is insensitive to light so it can be used intravenously more easily. Moreover, the combination of no tachycardia and maintained CO and CorBF after Nc during I anesthesia suggests that Nc might be the DHP-CB of choice under these circumstances. A similar effect was seen in patients with N_2O narcotic anesthesia[4]. Our data also show that administration of I results in an increase in Nc plasma concentrations, as halothane does for the plasma concentrations of another calcium channel blocker, verapamil[5].

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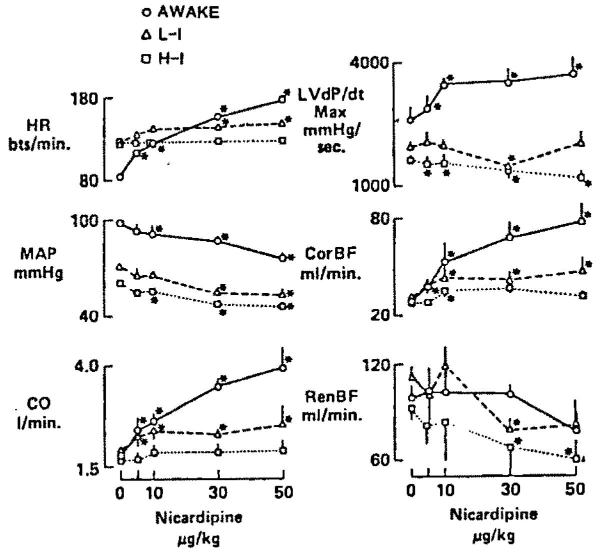

*p<0.05 vs control

Figure 1. The hemodynamic effects of Nc awake and during L-I and H-I.

Title: MYOCARDIAL METABOLISM AND HEMODYNAMICS IN HYPERTENSIVE CORONARY PATIENTS GIVEN FENTANYL-ENFLURANE ANESTHESIA.

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Introduction. Fentanyl-enflurane can induce mild hemodynamic depression but preserve myocardial oxygen balance in normotensive patients (pts.) having coronary artery bypass grafts (CABG).[1] During anesthesia blood pressure (B.P.) is often labile in hypertensive pts., so we studied the ability of this drug combination to produce smooth hemodynamic control in 10 treated hypertensive pts. Coronary sinus blood flow (CSBF), myocardial oxygen consumption (MVO_2) and lactate extraction (MLE) were also measured.

Methods. Informed consent and Ethics Committee approval were obtained. Six men and 4 women required CABG, but had normal ventricular function: mean EF=0.67, LVEDP=10 mm Hg, NYHA Class III - 8 and Class IV - 2 pts. Eight were taking betablocking and 4 Ca blocking drugs; 3 were also taking another antihypertensive drug. All drugs were continued until operation. Mean age was 60.3 years and weight 74.6 Kg. After diazepam and morphine premedication (mean 12 and 13.5 mgs), a radial artery cannula and 2 thermodilution internal jugular vein catheters were inserted under local anesthesia: one a PA catheter, one the Ganz catheter inserted into midcoronary sinus under fluoroscopy. Each study measured cardiac index (C.I.), CSBF, central and arterial pressures plus arterial and CS samples for Hb, O_2 saturation, lactate content. Studies were done before induction, 6 times during anesthesia and at 1 and 24 hours afterward.

Induction began with 30 µg/kg of fentanyl IV, with O_2-enflurane (mean conc. 1%) also needed in 7 pts. to reduce systolic pressure by 30% for 10 minutes before study 2. Enflurane (up to 4%) was continued after intubation to keep B.P. normal.

Results. Heart rate was unchanged on induction and intubation. Mean art. pressure (MAP) was reduced (103→67) on induction, was kept normal during anesthesia and was below awake level postop. NTG drip was given to decrease B.P.: during bypass - 4 pts., postbypass - 3 pts. C.I. remained decreased from induction through the 1 hour study: PC wedge pressure fell before bypass only. Stroke work (SWI) fell 49% on induction and remained well below awake level. Systemic vascular resistance decreased only on induction and increased after chest closure and at the 1 hour postop study. CSBF was higher than in the normotensive group,[1] before induction and after anesthesia. CS-O_2 content increased 31% on induction and stayed elevated until sternotomy. MVO_2 decreased throughout anesthesia. MLE continued until sternotomy with production continuously present in 1 pt. from awake through bypass. ST depression (mean 3.5 mm), present in 6 pts. awake, decreased to 1.5 mm postinduction; 4 other pts. developed ST segment elevation before bypass.

Discussion. Even with preop antihypertensive regimens and heavy premed, B.P.'s were elevated before induction. With fentanyl-oxygen-enflurane induction, MAP and C.I. fell as did SWI, CBF and MVO_2. Labile B.P. was seen in 3 pts. and most required no NTG during anesthesia; only 3 pts. needed vasodilation postop. Other than 1 pt. with lactate production before bypass, MLE continued and ST segments improved: evidence of better oxygenation. This drug combination effectively maintained hemodynamic depression and myocardial oxygen balance during and after anesthesia in long term hypertensive CABG pts.

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Mean ± S.D. n = 10	AWAKE	POST INDUCTION	POST INTUBATION	POST STERNOTOMY	POST BYPASS	ICU	
						1 HOUR	24 HOURS
RATE beats/min	71±13	71±14	70±11	68±13	79±11 x	77±11 x	92±12 x
MAP mm Hg	103±17	67±9 o	73±14 o	86±12 x	72±12 o	95±8	92±10
PC WEDGE mm Hg	16±14	11±8 x	9±5 x	10±6 x	10±4	11±7	8±3 x
CI $L/m/m^2$	2.9±0.7	2.4±0.4 x	2.4±0.4 x	2.1±0.6 x	2.5±0.5 x	2.1±0.8 x	3.1±0.8
SWI gM/m^2	72.3±19.1	36.8±8.8 o	41.1±12.3 o	42.7±10.3 o	35.2±7.2 o	37.6±12.5 o	54.9±17.6
SVR $dynes\cdot sec\cdot cm^{-5}$	1508±464	1128±252 x	1257±375	1798±625	1181±441	1969±494 x	1249±448
CSBF ml/min	177±89	123±74 x	101±55 o	83±51 o	129±47 x	226±130 o	247±85 o
CSO_2 CONTENT ml/dl	7.4±1.8	9.7±2.1 o	9.0±1.7 o	7.5±2.1	6.5±1.8 x	7.6±1.4	8.3±1.1
MVO_2 ml/min	17.1±8.9	9.3±6.9 x	7.3±4.2 x	6.8±4.4 x	5.2±2.2 x	16.2±9.6	18.4±9.4
MLE %	32±19	25±19	28±11	14±32	7±8	16±7	2±38
HEARTS PRODUCING LACTATE	1	1	1	1	2	0	2

x $p<.05$ o $<.005$

Title: AUTOMATED ACUTE NORMOVOLEMIC HEMODILUTION REDUCES BLOOD TRANSFUSION REQUIREMENTS FOR SPINAL FUSION

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Introduction. Currently, the three techniques of autologous blood transfusion are predonation, intraoperative salvage and acute normovolemic hemodilution with intra or postoperative reinfusion. The advantages of hemodilution include the reinfusion of blood with functional platelets and coagulation factors, and possible reduction of surgical blood loss. Our aims were to examine the efficacy, safety and reliability of intraoperative automated acute normovolemic hemodilution (AANH) in patients undergoing spinal fusion.

Methods. Automated acute normovolemic hemodilution was performed in 12 consecutive patients undergoing spinal fusion with instrumentation for scoliosis. Institutional approval and individual informed consent were obtained. Following induction of anesthesia and placement of arterial and central venous or pulmonary artery catheters, the patients were placed in the prone position and AANH was performed. AANH was rapidly achieved using an IBM-2997 blood cell separator (duration 35.3 ± SE 2.5 minutes). With the centrifuge bypassed, whole blood was removed from the patient via a central vein or arterial line, and anticoagulant added (ACD-A). Concurrently, lactated Ringers was infused via a venous line. The target hemodilution hematocrit was 20%. The blood was collected for storage at room temperatures (less than 6 hours) and was returned prior to the termination of surgery. Cardiorespiratory and hematologic variables and urine flow were measured. In addition, a sequential pairwise retrospective study, based on body weight and preoperative angle of curvature, was undertaken to compare blood loss, and homologous blood component transfusions in patients undergoing similar surgery. Standard parametric and non-parametric statistical methods were used.

Results. The results will be presented as 1) automated acute normovolemic hemodilution variables, 2) hemodynamic and hematologic variables during surgery and 3) comparison between prospective and retrospective series of the blood loss and homologous transfusion. The automated acute hemodilution procedure variables for 12 patients (age 11.7 ± 1.1 years, weight 40.8 ± 4 kg, blood volume 2.39 ± 0.29 liter) are listed in Table 1. The correlation between target and actual hematocrits was r = 0.75 ($p < 0.05$). The replacement rate was 99 ± 8 ml/min and the ratio of crystalloid replaced to blood withdrawn was 1.97 ± 0.4. The immediate posthemodilution significant hemodynamic changes were central venous pressure and heart rate (FIGURE 1).

Table 1: Automated acute normovolemic hemodilution procedure variables, mean ± SE, n = 12

Blood/ACD-A collected (liter)	Crystalloid replacement (liter)	Hematocrit Pre-dil. (%)	Hematocrit Post-dil. (%)
1.20 ±0.14	2.40 ±0.30	38.3 ± 1.3	21.9 ± 0.7

In the prospective series the intraoperative hemodynamic, respiratory, and hematologic variables were stable and urine flow adequate throughout in 10 of 12 patients (FIGURE 1). The immediate postoperative hematocrits and platelets were 28.7 ± 1.2% and 263 ± 31 (x 10^3), respectively. The pairwise retrospective study demonstrated (age 16.4 ± 2.4 years, weight 46. 4 ± 4.2 kg) that hemodilution reduced blood loss and reduced or eliminated transfusion of homologous blood or components (mean ± SE) (TABLE 2). In addition, the duration of surgery in the retrospective and prospective studies were 8.03 ± 0.52 and 5.68 ± 0.54 hours ($p < 0.01$), respectively. In both series there were 2 lumbar meningomyelocele patients who had massive blood loss, and homologous blood and component transfusions. Their hemodynamic, hematologic and blood transfusion data were similar.

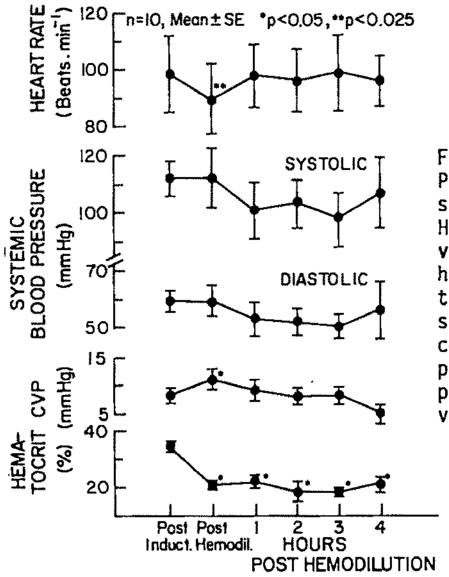

FIGURE 1. Prospective series: Hemodynamic variables and hematocrit throughout surgery and comparison with postinduction prehemodilution variables.

Table 2: Retrospective and prospective series

Series	Blood loss (liter)	Homologous Blood Components: Units PRBC	FFP	Platelets
Retrospective n = 10	5.49 ±0.98	8.6 ±1.6	1.8 ±0.7	1.2 ±0.8
Prospective n = 10	1.70 ±0.39	<1 0	0 0	0 0
p value	<0.005	<0.001	<0.025	<0.01

Discussion. The data showed that acute normovolemic hemodilution was well tolerated in major surgery. There were no complications associated with the hemodilution, monitoring or the anesthetic technique. The postoperative hematocrits and platelet counts were satisfactory. Furthermore, automation of this protocol using the IBM-2997 or similar device was demonstrated to improve speed, safety and provide accurate control of the hemodilution process.

Title: COMPARISON OF PERI-OPERATIVE FACTORS AFFECTING POTASSIUM REQUIREMENTS BETWEEN CABG VS VALVE PATIENTS DURING POST-OPERATIVE PERIOD

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Introduction: The pharmacological profile of patients undergoing CABG and VALVE surgery is distinctly different (1,2). The effect of B-blockers, digitalis and diuretics on serum potassium levels during the CPB have been studied (1,2). However, the influence of these drugs on the post-operative requirements have not been compared. The purpose of this study is to compare the peri-operative factors influencing potassium requirements during post-operative period between CABG (B-blocker-pretreated) Vs Valve (digitalis-pretreated) patients.

Methods: The charts of 93 patients who underwent elective CABG and 54 patients who underwent Valve replacement (mitral and Aortic) during one year were reviewed. The preoperative drug profile, intra-operative and post-operative data was collected. All patients were premedicated with morphine 0.1 mg/kg and Diazepam 0.2 mg/kg one hour prior to surgery. Anesthesia was induced with incremental doses of morphine, diazepam and thiopental. Tracheal intubation was achieved with succinylcholine. Anesthesia was maintained with O_2, N_2O (50%) and enflurane 1%-2%. CPB was established in standard fashion. Plasmolyte (2500 cc) was used as priming solution. Myocardial preservation was accomplished with cold K^+ cardioplegia 930 mEq/L). Mannitol or KCl was not infused during CPB. Fluids and blood were given as required during CPB separation. At the end of surgery all patients were mechanically ventilated in ICU. CPB time, urine output in operating room, urine output in ICU for 24 hrs., and total potassium replaced for 24 hrs. in ICU were recorded. PH and PCO_2 were maintained within normal limits. The data was then compared between CABG and Valve patients utilizing student's 't' test.

Results: Results are given in the tables below.

Discussion: Changes in the serum potassium levels during and after open heart surgery have been extensively studied (1). Recently, paradoxical increase in serum potassium during CPB has been reported in B-blocked patients (2). However, the extension of this effect into the post-operative period has not been reported. Our study indicates a significantly higher potassium requirement among CABG patients compared to valve patients. This may be due to the influence of B-blockers on K^+ homeostasis, by inhibiting the influx of K^+ into the muscle cells subjecting the cation for excessive urinary loss (2). The need for K^+ replacement in our patients on digoxin and diuretics is consistent with the earlier findings (1).

A linear relationship between the CPB time and K^+ replacement has been shown in the previous studies (1). A similar finding has been observed in our study indicating excessive K^+ requirements in CABG patients who had prolonged CPB time. Also, a decreased K^+ requirement was seen in valve patients with a decreased CPB time. The urine output both in the operating room and in ICU has been significantly higher in CABG group in our study. Although the exact reason for this is not clear, this might have resulted in an increased urinary loss of K^+ in this group.

Thus, our study reveals a significantly higher K^+ requirement in patients who have been on B-blockers (CABG) compared to patients on digoxin and diuretics (valve). Also, the CPB time, urine output in OR and in ICU have significant influence on the K^+ requirements in the post-operative period.

Results:

Table 1. Comparison of Preoperative Profile between CABG vs Valve Patients

	CABG n=93		Valves n=54	
Beta-blocker	75	(80.65%)	-0-	
Hydrochlorothiazide	24	(25.81%)	-0-	
Digoxin + Furosemide	-0-		36	(66.67%)
Age [mean]	57.91		53.09	

Table 2. Comparision of Factors affecting K+ replacement between CABG vs Valve patients

Factor	CABG (n=93)	Valves (n=54)	t value	p value
K+ replaced (in 24 hrs)	50.16± 3.60	35.83± 4.24	2.50	0.014
CPB time	97.95± 3.22	77.94± 4.42	3.74	0.000
U.O. (OR)	929.34± 62	549.59±44	4.95	0.000
U.O. (ICU)	1876.62±103	1424.27±65	3.69	0.000

References: 1. Babka R, Pifarre R: Potassium replacement during cardiopulmonary bypass. J Thorac Cardiovasc Surg 73:212-215, 1977

2. Bethune DW, McKay R: Paradoxical Changes in serum potassium during cardiopulmonary bypass in association with non-cardioselective Beta-blockade. The Lancet 2:380-381, 1978

Title: POTASSIUM REQUIREMENTS FOLLOWING CORONARY ARTERY BYPASS GRAFT (CABG) SURGERY: THE EFFECT OF PERIOPERATIVE FACTORS.

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Introduction: The requirements for potassium vary widely in the immediate period following CABG surgery (1). Although the reasons for this are multifactorial the effect of perioperative factors on these requirements have not been studied in patients undergoing CABG surgery. The purpose of this study is to analyze the influence of perioperative factors on the postoperative potassium requirements in patients undergoing CABG surgery.

Methods: The charts of 93 patients who underwent elective CABG surgery during one year were reviewed. All patients were premedicated with morphine 0.1mg/kg and diazepam 0.2mg/kg one hour prior to surgery. Anesthesia was induced with incremental doses of morphine, diazepam and thiopental. Tracheal intubation was carried out with succinylcholine. Anesthesia was maintained with O_2, N_2O (50%), enflurane (1-2%) and pancuronium bromide. CPB was instituted in the standard fashion. Plasmolyte (2500cc) was used as a priming fluid in the bubble oxygenator. Systemic hypothermia (24-26°c) was maintained. Myocardial preservation was accomplished with intermittent infusion of clear cardioplegia (30 mEq/L) at 4°C. Arterial blood gases, urine output and serum K^+ were measured during CPB. Potassium was not infused during CPB. Fluids and blood were given as required during CPB separation. Following surgery, all patients were admitted to SICU and routine blood work was done including serum K^+. Potassium was given intravenously for serum levels below 3-5 mEq/L. The total K^+ replaced during the next 24 hours was measured. CPB time, urine output in the operating room and in ICU were measured. Patients were then divided into two groups viz:diabetics/nondiabetics:Diuretic/nondiuretics and data was analyzed for differences in the K^+ requirement. Also the effect of CPB time, urine output in OR, and in SICU, on the total K^+ replaced was analyzed. Data was analyzed utilizing Pearson's correlation coefficient, "t" test on Pearson's r-value.

Results: Please see tables.

Discussion: In the previous studies prior to the use of cold K^+ cardioplegia, the requirements for K^+ have been high during the postoperative period (113 mEq/L) (1). In our study, the potassium replaced during the first 24 hours after surgery is 50.16 ± 3.6 mEq/L. This decreased requirement may be due to the use of cold K^+ cardioplegia solution. Persistent hyperkalemia following the use of K^+ cardioplegia has not been reported (2). However, hyperkalemia at the termination of CPB has been reported in a large number of diabetic patients due to derangements of K^+ homeostasis (3). No such incidents were recorded in our diabetic patients. The K^+ requirements between diabetic and nondiabetic patients were not significantly different in our study. Similarly, the K^+ replaced in our patients who were on prior diuretic therapy was not excessive compared to nondiuretic patients. Excessive urinary loss of potassium has been reported in the diuretic group in the previous study (1).

Contrary to the findings of Babka, CPB time, urine output in OR and SICU have no significant effect of the total K^+ replaced in our study. Most of the previous studies included patients with mixed procedures viz, CABG, MVR, AVR. Majority of our CABG patients were on combination treatment of beta-blockers and thiazides. Whether or not this influenced the K^+ homeostasis in our study is hypothetical.

In summary, our data indicate that the variables analyzed (diabetics/diuretic/CPB time/urine output OR/urine output SICU) have no significant effect on the K^+ replaced during the first 24 hours following CABG surgery.

Table 1. Analysis of K^+ requirements in CABG patients: Influence of Diabetes and Diuretics.

	Pre-op K+	Immediate Postop K+	K+ Replaced	Pearson's r	t test
Diabetics (n=18)	4.20±0.1	3.89±0.14	47.22±8.47	-0.42	2.0
Non-diabetics(n=75)	4.20±0.05	3.66±0.10	33.67±5.06	-0.58	0.36
Diuretics (n=27)	4.02±0.83	3.50±0.08	56.67±7.52	-0.50	0.74
Non-diuretics(n=66)	4.29±0.05	3.70±0.08	48.86±4.15	-0.58	0.39

Table 2. Analysis of CPB time and urine outputs on K+ requirements (N=93) in CABG patients.

CPB time	Urine output (OR)	Urine output (SICU)	K+ replaced in 24 hrs
97.95±3.22	929.34±62	1876.62±103	50.16±3.60
(Pearson's r):			
0.06	0.21	0.14	

(Multiple correlation coefficient R=0.28, R^2=0.08)

References: 1. Babka R, Pifarre R: Potassium replacement during cardiopulmonary bypass. J. Thorac Cardiovasc Surg 73:212-215, 1977

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Title: NEUROTENSIN AND VASOACTIVE INTESTINAL PEPTIDE LEVELS DURING ORTHOTOPIC LIVER TRANSPLANTATION

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Introduction

During orthotopic liver transplantation, revascularization of the implanted liver has been associated with a number of untoward cardiovascular and hemodynamic sequelae, including hypotension, ventricular dysrhythmias, and cardiac arrest. The cause of the consistent hypotension, in the absence of dysrhythmias, noted upon revascularization remains unknown, although transient depression of the cardiovascular system secondary to the release of acid metabolites from previously clamped vascular beds and the release of K^+ and cold perfusate from the donor liver has been postulated (1).

In our patients, hypotension has been most consistent and significant following reperfusion of the portal vein despite adequate filling pressures, normal blood gases, ionized calcium and K^+.

A hypothesis currently being investigated is that gut ischemia during the anhepatic phase could result in accumulation of vasoactive substances in the portal system that, upon release, cause hypotension. Vasoactive Intestinal Peptide (VIP) and Neurotensin (NT), both present in the gut, have been shown to cause severe hypotension (2,3).The measurement of VIP and NT was undertaken to determine if they could contribute to the blood pressure changes. The preliminary results are reported.

Methods

Institutional approval was obtained for the study. During liver transplantation, the following specimens were obtained: Specimen I, arterial baseline following induction of anesthesia; II, portal venous sample obtained shortly after clamping of portal vein; III portal venous sample just prior to unclamping; IV arterial sample one minute after unclamping; V arterial sample three minutes after unclamping; VI arterial sample five minutes after unclamping. A RIA was performed for VIP and NT.

Results

VIP Concentrations (pg/ml)[a]

Specimen	I	II	III	IV	V	VI
1	22.5	32.5	40.0	32.5	27.5	30.0
2	15.0	32.5	30.0	15.0	11.2	7.5
3	35.0	40.0	40.0	32.5	30.0	35.0
4	5.0	0.0	15.0	15.0	17.5	15.0
Mean	19.5	26.3	31.3	23.8	21.6	18.1
	±	±	±	±	±	±
SEM	6.3	8.9	5.9	5.0	4.4	5.9
P Value[b]			0.3	0.3	0.6	0.6

NT Concentrations (pg/ml)[a]

	I	II	III	IV	V	VI
1	31.0	20.0	15.6	21.8	16.2	19.5
2	24.0	17.0	15.6	22.5	21.0	24.0
3	21.9	18.0	17.3	13.5	17.5	17.3
4	16.0	22.5	15.0	15.0	6.3	12.5
5	16.0	7.5	34.0	12.0	13.5	12.0
6	18.0		17.0	5.0	13.8	11.3
7	24.0		25.0	16.0	14.0	11.0
Mean	21.5	17.0	19.9	15.1	14.6	15.3
	±	±	±	±	±	±
SEM	2.0	2.5	2.6	2.2	1.7	1.9
P Value			N.S.	.008	.007	.012

a) Average of 2 determinations
b) Student's paired 2-tailed t-test

Discussion

All patients experienced a drop of 20 to 30 mmHg systolic blood pressure upon unclamping of the portal vein. These drops in blood pressure were seen despite volume loading, and correction of acid-base and electrolyte abnormalities prior to unclamping. The results clearly fail to implicate VIP and NT as contributing factors in reperfusion hypotension. Comparison of samples II and III shows no significant increase in VIP and NT concentrations of portal venous blood during portal vein clamping. Likewise, comparison of sample I with samples IV, V, and VI shows no increase in systemic VIP and NT concentrations after portal vein unclamping. In addition, all of the measured VIP and NT concentrations were within normal limits (<50 pg/ml).

References

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3. Rioux F, Kerouac R, Quition R, St.-Pierre S. Mechanism of the cardiovascular effects of neurotensin. Ann NY Acad Sci 1982; 400:56-74.

Title: EFFECTS OF THIOPENTAL ON CEREBRAL EVOKED POTENTIALS

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Introduction: Intraoperative monitoring of somatosensory evoked potentials (SSEP) can provide information about the integrity of sensory tracts at risk during spinal surgery. It may also warn of neurologic depression caused by hypoxia or hypoperfusion. Anesthetic agents have been shown to cause changes in SSEP responses [1,2] but not all of these effects have been well defined. Sodium thiopental is a commonly used induction agent in patients undergoing intraoperative monitoring and during several studies of the effects of other agents on SSEP.[3] This study was designed to investigate the effects of a single dose of sodium thiopental on the latency and amplitude of the median nerve SSEP.

Methods: Nine ASA Class I and II patients scheduled for lumbar surgery with intraoperative SSEP monitoring were studied using this institutionally approved protocol. Unpremedicated patients had intravenous lines established and the calculated overnight fluid deficit was replaced. Monitoring included an electrocardiogram, blood pressure cuff, end-tidal CO_2, and precordial stethoscope.

Cortical (C_3', C_4' to F_z) and cervical (second cervical vertebra to F_z) median nerve SSEP were recorded using two hundred fifty repetitions of unilateral stimulation. Stimulation at 5.7 or 8.7 Hertz using a bar electrode at the wrist was with 300 microsecond constant current pulses at 1 milliamp above motor threshold. The responses acquired from collodion affixed disc electrodes (shoulder ground) were filtered (bandpass 5-250 H_z) and averaged over 50 milliseconds using a Nicolet CA-1000. Baseline reponses were obtained in duplicate and then the patients were given thiopental 4 mg/kg intravenously over 30 seconds. SSEP responses were recorded every minute for at least eight minutes until the patient began to awaken. During the recording period, ventilation with 40% oxygen in air was assisted by mask to maintain end-tidal pCO_2 40-45 torr. No patient had significant blood pressure or pulse swings during the study period. SSEP recordings were analyzed to obtain the post stimulus latency of the cervical response and of P_1 (17 msec), N_1 (20 msec), and P_2 (26 msec) waves of the cortical response. Amplitude was measured peak to trough (N_1 to P_2) of the cortical response. SSEP latencies and amplitudes at 0,4,8 and 12 minutes were compared using the Friedman two-way analysis of variance; differences were confirmed with Wilcoxon matched-pairs signed ranks test.

Results: Shown in Figure 1 are the average cervical and cortical P_1, N_1 and P_2 absolute latencies for these patients during the study period. A statistically significant difference ($p<0.02$) was seen in the latencies of the cortical P_1 and N_1 responses. The average amplitude remained the same.

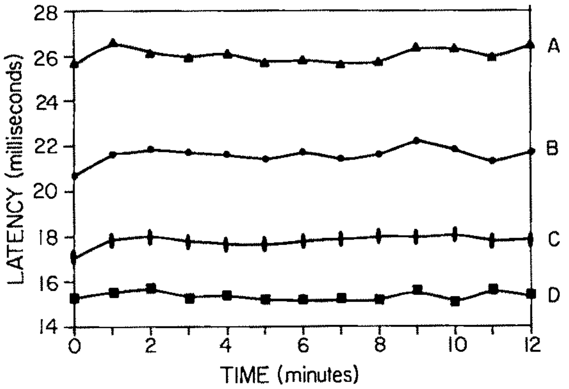

Figure 1. Average latencies in milliseconds versus time in minutes: A. Cortical P_2 B. Cortical N_1 C. Cortical P_1 and D. Cervical P_1.

Discussion. Clinical experience has indicated that sodium thiopental bolus during anesthesia is associated with a moderate change in the SSEP. This study suggests the effect of thiopental in unanesthetized and unpremedicated healthy patients is much less dramatic. Since essentially no change occurred in the response measured over the cervical spine, this location may be an excellent location for recording during bolus injections of this agent. The noted alterations in the cortical SSEP latency suggest the primary effect of thiopental is on neural conduction cephalad to the cervical spine. Further, the absence of significant amplitude reduction suggests a lesser effect on cortical neuronal function. This is compatable with a significant effect of thiopental on brainstem function.

References

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3. Pathal, KS, et al: Effects of fentanyl and morphine on intraoperative somatosensory cortical-evoked potentials. Anesth Analg 62: 841-845, 1983.

Title: THE EFFECTS OF SUFENTANIL ON MEDIAN NERVE SOMATOSENSORY EVOKED POTENTIALS

Authors: A Koht, M.D., MA Kimovec, M.D., TB Sloan, M.D., Ph.D., and AO Carlvin, N.D.T.

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Introduction. Intraoperative monitoring of somatosensory evoked potentials (SSEP) has gained acceptance as a monitoring tool in spinal surgery. Anesthetic agents can adversely affect the SSEP signals. A narcotic based anesthetic technique is thought to have the least depressant effect.[1] Sufentanil, a recently released synthetic narcotic, is gaining acceptance for anesthesia in these operations, but its effects on SSEP have not been delineated. This study was undertaken to define those alterations subsequent to a 5 mcg/kg dose of sufentanil.

Methods. This institutionally approved study included fifteen ASA Class I & II patients, age 24-55, scheduled for lumbar or thoracic spinal surgery with SSEP monitoring. These patients were not given premedication and had their overnight fluid deficit replaced. Disc recording electrodes were secured using collodion at Fz, C3', and C4' of the International 10-20 system as well as posterior to the second cervical vertebra. Stimulation at 8.7 Hertz was accomplished using 300 microsecond constant current impulses over the median nerve at the wrist using a bar electrode and current 1 milliamp above motor twitch. Two hundred and fifty responses were filtered (5-250 Hertz), amplified and averaged on a Nicolet CA 1000 signal averager. After recording duplicate baseline responses, anesthesia was induced with sufentanil 5 mcg/kg over 30 seconds and pancuronium 0.02-0.12 mg/kg as needed to ease chest wall rigidity. Ventilation was assisted or controlled with 100% oxygen to keep end-tidal CO_2 between 35-45 torr. Heart rate, blood pressure, and SSEP were measured at 1,2,3,4, 5,6,7, 8,9,12,15,18,21,24,27, and 30 minutes. At the end of the study period intravenous valium 10 mg and scopolamine 0.4 mg were given, and isoflurane (0.2-0.4%) begun. The response recorded over the cervical spine at 15 milliseconds (msec) and the three cortical waves, P_1 (17 msec), N_1 (20 msec), and P_2 (26 msec), were analyzed for changes in latency. Cortical amplitude was calculated from N_1 (trough) to P_2 (peak). All were compared at baseline, and at 8, 12, 18 and 24 minutes using the Friedman two-way analysis of variance. Differences were confirmed with a signed ranks test.

Results. Shown in Figure 1 are the average latencies of the four peaks measured. The latency increases of cortical waves N_1 and P_2 were statistically significant ($p < 0.01$).

Of the fifteen patients studied, twelve patients had a decreased cortical amplitude and two had an increase. The average amplitude tended to decrease to approximately 60% of the baseline value which was statistically significant ($p < 0.01$).

Discussion. The changes demonstrated in this study occurred during the first 8 minutes, following which the latency and amplitude were stable. Although statistically significant, the increase in latency was only 1-2 milliseconds. Amplitude reduction did not interfere with signal acquistion. These observed changes are thought not to be caused by fluctuations in blood pressure, ventilation or temperature as these physiological variables were not significantly altered during the study period.

Subsequent monitoring of posterior tibial nerve SSEP in these patients was accomplished easily using this baseline anesthetic technique. The above changes suggest that alterations in SSEP due to sufentanil are most likely to occur early following moderate bolus delivery, and subsequently remain stable.

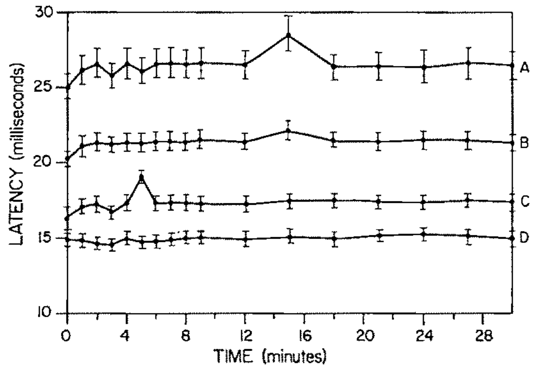

Figure 1. Average latency ($\pm$ SEM) following 5 mcg/kg sufentanil bolus.
A. Cortical P_2, B. Cortical N_1,
C. Cortical P_1, D. Cervical P_1

Reference

1. Pathak KS, Brown RH, Cascorbi HF, and Nash CL: Effects of fentanyl and morphine on intraoperative somatosensory cortical-evoked potentials. Anesth Analg 63:833-7, 1984.

Title: COMPARISON OF SUFENTANIL-DIAZEPAM AND FENTANYL-DIAZEPAM ANESTHESIA FOR INDUCTION

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Introduction: Diazepam alone produces minimal hemodynamic changes, but decreases in mean arterial pressure (MAP), systemic vascular resistnce (SVRI), and sometimes cardiac index (CI) have been reported when diazepam was used in combination with fentanyl.[1,2] Sufentanil has recently become available for clinical use, but the hemodynamic effects of the combination of sufentanil and diazepam have not been reported. The purpose of this study was to compare its hemodynamic effects to those of diazepam fentanyl anesthesia.

Methods: Seventeen patients undergoing coronary artery surgery were studied after institutional approval. The patients with moderate to severe left ventricular dysfunction or patients with hypertension were excluded. All monitoring lines were placed prior to induction of anesthesia. Heart rate (HR), systolic arterial pressure (SAP), MAP, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) and cardiac output were monitored. CI, stroke volume index (SVI), left ventricular stroke work index (LVSWI), SVRI and pulmonary vascular resistance index (PVRI) were calculated using standard formulae. Patients were preoxygenated. Following pretreatment of 1 mg of pancuronium (i.v.): Group 1 (S-D:n=7) received 10 μg/kg of sufentanil, and Group 2 (F-D:n=10) received 50 μg/kg of fentanyl both mixed with 0.1 mg/kg of pancuronium during a 4-6 minutes period intravenously. Subsequently, small increamental doses of diazepam (0.025 mg/kg) were administered up to 0.1 mg/kg for all patients. Patients received 3.3 ± 0.8 ml/kg of intravenous fluid prior to and during induction of anesthesia. Hemodynamic measurements were made prior to induction (C), following administration of sufentanil with pancuronium or fentanyl with pancuronium (D0), after 0.025 mg/kg (D1), 0.05 mg/kg (D2), 0.0725 mg/kg (D3), and 0.1 mg/kg diazepam (D4). In order to characterize the effect of diazepam superimposed on sufentanil or fentanyl, the changes of hemodynamic variables were expressed as percents of the values at D0. Changes of trends were examined using tests for linear trend between % changes in variables and cummulative doses of diazepam.

Results: There were no differences in all variables between the two groups at (C). Following administration of sufentanil or fentnayl, hemodynamic variables changed but there were no differences between the groups except SAP and MAP were higher in group 2. As the dosages of diazepam increased HR, MAP, PCWP, MAP, SVI and LVSWI decreased linearly in both groups (Table 1). SAP, MPAP and CI decreased linearly as the doses of diazepam increased, but there were significant differences in trends in those variables between the groups (Table 2). The slopes of SAP, MAP in group 2 were steeper than in group 1. The slope of CI in group 1 was steeper than in group 2. SVRI increased linearly in group 1 while unchanged in group 2 and there were significant differences in values at D3, D4 (Group 1: 109%, 114%, Group 2: 98%, 104%, respectively). CVP and PVRI did not changed following administration of diazpam.

Discussion: Our results suggests that the use of diazepam as an induction agent following sufentanil may cause dose related decreases in MAP and CI. The decrease of CI can be attributable to the decrease in preload and direct myocardial depression. An increase in SVRI induced by hypotension may lead to a vicious circle, aggravating myocardial depression. Diazepam following fentanyl also decreased MAP associated with a decrease in CI most likely due to both a decrease in preload and myocardial depression as the dosage of diazepam increased. Tomicheck[2] et al reported that diazepam in combination with fentanyl produced a decrease in MAP due to a decrease in SVRI without any changes in CI while a constant PCWP was maintained by fluid management (10-15ml/kg). Our patients received only 3.3 ml/kg of fluid during the peri-induction period. Therefore, the diffrence of the result can be attributable to the difference in fluid management. Since a very small dose of diazepam in combination with sufentanil or fentanyl produced significant hemodynamic changes and its changes were related to the dosage of diazepam, an intravenous administration of diazepam should be titrated with a small incremental dose (0.025 mg/kg) and fluid management is recommended during induction of anesthesia.

Reference:

1. Stanley TH et al: Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg 1978;57:411.

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Table 1. Linear trend between % changes in hemodynamic variables and cummulative doses of diazepam in over all patients.

	Regression line	r	p	Est. value at D4 (%)
HR	$y=-2.43x+103.7$	-0.73	<0.001	92
PCWP	$y=-4.19x+101.9$	-0.74	<0.0001	81
MAP	$y=-3.69X+102.9$	-0.77	<0.0001	84
SVI	$y=-2.73x+102.5$	-0.71	<0.005	89
LVSWI	$y=-5.67x+104.9$	-0.78	<0.0001	77

Table 2. Linear trend between % changes in hemodynamic variables and cummulative doses of diazepam.

		Regression line	r	p	Est. value at D4 (%)
SAP	G1	$y=-3.02x+102.3$	-0.70	<0.05	87
	G2	$y=-4.71x+104.5$	-0.85	<0.001	80
CI	G1	$y=-5.14x+103.8$	-0.91	<0.005	78
	G2	$y=-4.99x+106.9$	-0.92	<0.0001	82
MPAP	G1	$y=-2.72x+ 99.3$	-0.81	<0.05	86
	G2	$y=-4.43x+103.3$	-0.96	<0.0001	81
SVRI	G1	$y=+3.40x+ 96.5$	+0.80	<0.05	114
	G2	--------	-0.40	NS	100

Est. value: estimated value from regression line

Title: PROSTACYCLIN AND THROMBOXANE CHANGES ASSOCIATED WITH PROTAMINE ADMINISTRATION

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Introduction Following protamine sulfate (PS) administration, significant decreases in systemic vascular resistance (SVR) have been reported (1) and in patients with pulmonary hypertension (PAH), catastrophic pulmonary vasoconstriction has been observed (2). Thromboxane (TxA_2), a potent vasoconstrictor, is capable of producing increases in pulmonary vascular resistance (PVR). Conversely, prostacyclin, a potent vasodilator, could cause a decrease in SVR. In vitro and animal studies suggest that heparin-protamine complexes stimulate thromboxane synthesis (3). This study was designed to test the hypothesis that heparin-protamine complexes activate the arachadonic acid pathway, and that the products of these pathways are responsible for the observed hemodynamic reactions from protamine administration.

Methods After institutional approval and informed consent was obtained from each patient, ten adults with pulmonary hypertension (mean pulmonary arterial pressure at cardiac catheterization > 30 mmHg) undergoing elective mitral valve replacement were studied. Patients taking known cyclooxygenase inhibitors or who were septic were excluded from the study. Anesthesia was induced with fentanyl 50-100 mcg/kg, pancuronium 0.025 to 0.1 mg/kg and/or metocurine 0.1-0.4 mg/kg. The patients were monitored with EKG leads II, V_5, and radial arterial and pulmonary arterial catheters. Baseline hemodynamic measurements and arterial blood for thromboxane and prostacyclin analysis were obtained after the termination of cardiopulmonary bypass. PS was infused at 0.8 mg/kg/min via the central venous port of the Swan-Ganz catheter. One mg of PS was administered for each mg of heparin that had been given. Hemodynamic and prostanoid measurements were obtained 5, 10, 15, and 30 minutes after the PS infusion was started. Throughout the study period, left atrial filling pressures were maintained at a constant level by infusion of autologous blood. Plasma measurements of circulating stable metabolites of thromboxane A_2 and prostacyclin, thromboxane B_2(TxB_2) and 6-keto $PGF_{1\alpha}$, respectively, were performed by a double-antibody radioimmunoassay(4). Data are expressed as mean ± 1 SE. Significance was tested by the Student's paired t-test.

Results As shown in the table, there were no significant changes in either prostanoid level during the study period. However, one patient started with an elevated baseline of TxB_2 and within 5 minutes doubled the level in response to protamine (0.650- 1.200ng/ml). Five minutes after PS, this patient also had an elevated 6-keto $PGF_{1\alpha}$ level (0.720ng/ml). No patient had a significant hemodynamic response to the PS administration and there were no changes in heart rate, SAP, pulmonary artery pressure, cardiac output, SVR, and PVR.

Discussion In our study, no serious hemodynamic reactions to protamine were noted, and no significant changes in prostanoid levels were observed due to the large standard errors. Of particular note, one patient had a grossly elevated TxB_2 baseline level which subsequently doubled after PS, yet the patient manifested no hemodynamic instability. Perhaps there were no hemodynamic problems because of the concurrent increase in 6-keto $PGF_{1\alpha}$. In patients who have experienced hemodynamic reactions to protamine, it is possible that no compensatory rise in this compound occurred. It is clear from this patient that not every rise in TxA_2 will lead to hemodynamic compromise, and that caution must be exercised in assigning a causitive role for TxA_2 in protamine-induced pulmonary vasoconstriction. Studying a larger population of patients receiving protamine intraoperatively will serve to form a rational basis for better understanding of this untoward drug reaction, and designing the most appropriate therapy for its treatment or prevention.

References
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TABLE Prostanoid Levels

TxB_2 (ng/ml)

Baseline	5 min	10 min	15 min	30 min
0.24±.05	0.40±.13	0.36±.08	0.33±.06	0.25±.07

6-keto-$PGF_{1\alpha}$ (ng/ml)

Baseline	5 min	10 min	15 min	30 min
0.21±.07	0.20±.08	0.16±.04	0.15±.05	0.15±.05

all non-significant

TITLE: PHARMACOKINETIC STUDY OF ISOFLURANE IN MAN - UPTAKE INTO BRAIN

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INTRODUCTION

Due to its low solubility in blood, induction with isoflurane can be achieved readily with rapid rise in end-tidal and arterial tensions.[1,2] However, uptake into and equilibration with individual organ compartments has not been studied. This is particularly relevant for the brain since this is the organ where the anesthetic exerts its action. Moreover, since isoflurane may have a brain protective effect, it is important to know the time course required for the brain to achieve equilibrium with the arterial tension of isoflurane. This study is an attempt to address this issue by studying the arterial cerebral venous difference in isoflurane tension during wash in.

Method

The study was approved by the institutional Human Ethics Committee. Six patients (ages 41-73) undergoing craniotomy for cerebral aneurysm surgery were included in the study. In all patients anesthesia was induced with fentanyl 1-2μg•kg^{-1}, thiopental 4–6 mg•kg^{-1}, and endotracheal intubation was accomplished following the administration of lidocaine 1.5 mg•kg^{-1} and succinylcholine 1 mg•kg^{-1}. Patients were then mechanically ventilated with an air/oxygen mixture, with an end-tidal CO_2 between 32 and 34 mmHg. Anesthesia was maintained with intermittent doses of fentanyl, thiopental and pancuronium until isoflurane was introduced as described below. Following placement of appropriate monitors including ECG and arterial catheter, a 16 gauge catheter was placed in the internal jugular bulb by cannulating the right internal jugular vein and advancing the catheter in a retrograde fashion. Blood sampled from this catheter was deemed to reflect cerebral venous drainage. Following stabilization of the patient, isoflurane was administered at an inspired concentration of 1.35% and simultaneous arterial (A) and cerebral venous (CV) samples were collected at times 0, 1, 3, 5, 10, 20, 32, and 45 mins after administration of isoflurane. In addition, in 5 patients simultaneous cerebral spinal fluid (CSF) samples were also obtained from the lumbar subarachnoid catheter for the determination of the CSF tension of isoflurane. The inspired isoflurane concentration was monitored with mass spectrometry and the A, CV and CSF samples analyzed with gas chromatography. Data from all 6 patients were pooled, and two-way analysis of variance was used to assess differences between A, CV and CSF samples.

Results

The rise of A, CV and CSF tension expressed as a fraction of inspired tension is shown in the figure. As expected, there was a rapid rise in A tension, followed by the CV tension with the CSF tension lagging behind. In all 6 subjects, the CV tension approximated A tension between 20 to 32 mins and there was no statistical difference between A and the CV tension from 20 mins on. The CSF tension, on the other hand, was substantially below the A tension even after 45 mins. Similar observation had been reported recently.[2]

Discussion

Assuming that the CV samples were not contaminated by systemic venous values, the equilibration between A and CV tension implies equilibration with the brain with no further uptake of isoflurane. That contamination likely did not occur was supported by the fact that arterial cerebral venous equilibration occurred in all 6 subjects within a time frame inadequate for arterial systemic venous equilibration. The actual time required for brain equilibration for any individual patient is dependent on cerebral blood flow, solubility of isoflurane in the brain and the brain mass. Although CBF was not studied, this was assumed to be normal since all patients were neurologically intact preoperatively and were not suspected to have any flow impairment. In addition, previous studies in humans suggest that CBF is unchanged by isolfurane at this depth. Although intra-cerebral regional distribution was not addressed in this study, we conclude that the brain as a whole compartment is equilibrated with arterial blood within 20 to 32 mins of isoflurane administration. Lumbar CSF tension, on the other hand, lags substantially behind and does not reflect brain tension. These data further suggest that if the brain protective aspect of isolfurane is to be exploited, optimal protection can be achieved after 20 mins of isoflurane administration.

References

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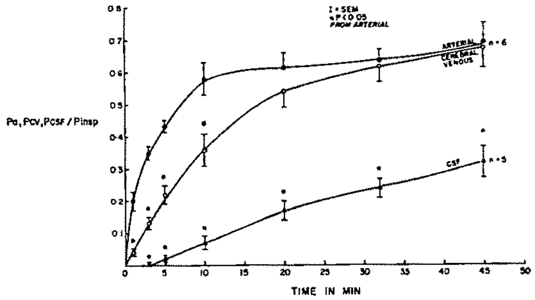

TITLE: MONITORING OF SOMATOSENSORY EVOKED RESPONSES DURING CARDIOPULMONARY BYPASS – THE INFLUENCE OF TEMPERATURE

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INTRODUCTION

Intraoperative monitoring of somatosensory evoked responses (SSEP) can provide important information during procedures where the central nervous system is at risk. However, it is necessary to delineate the influence of anesthesia and body temperature in order to allow intelligent interpretation of intraoperative SSEP recordings. Provided that anesthetic depth is maintained constant, the influence of anesthesia may be reasonably discounted, but body temperature may not be as easily maintained constant. The effect of mild hypothermia on SSEP has recently been investigated showing little influence when the body temperature did not fall below 35°C.[1] Below this temperature, however, the latencies increased significantly.[2] In this study we assess the feasibility of monitoring SSEP during hypothermic cardiopulmonary bypass and the influence of temperature on SSEP latency and amplitude.

Method

The study was approved by the institutional Ethics Committee and SSEP was recorded from 10 patients undergoing coronary artery bypass graft surgery. A Nicolet CA 1000 averager was used for the recording of SSEP. Recording electrodes were placed on the parietal cortex (C3', C4'), Erb's point, and C_7 spine in reference to forehead. The median nerves were stimulated with a square wave at 200 μsec duration and 15 mamp intensity using Grass needle electrodes. At least 256 responses were averaged. Bilateral recordings were initially obtained during normothermia to ensure symmetry and subsequently only unilateral recordings were obtained. The body temperature was monitored with a nasopharyngeal probe. Anesthesia was induced with fentanyl (50-100 $\mu g \cdot kg^{-1}$) and pancuronium and maintained with fentanyl, air and oxygen. SSEP was recorded immediately following induction of anesthesia, during cooling, bypass and subsequent rewarming. Both latency and amplitude of the peaks recorded over Erb's point (N10), C_7 (N13) and parietal cortex (N20) were analyzed with linear regression and separate analysis was performed for cooling and rewarming data.

Results

Due to technical problems, satisfactory data were only recorded in 8 patients. The change in amplitude and latency with temperature during cooling are shown in the Table. Increase in latency with temperature was noted with all peaks with significant linear correlation ($p < 0.01$). The increase in central conduction time (N20-N13, N20-N10) followed a similar trend after the body temperature decreased below 35°C. The increase in central conduction time exceeded the increase in peripheral conduction (N10 latency). The change in amplitude was not uniform, with N13 and N20 showing progressive decrease in amplitude with decrease in temperature, but an increasing amplitude with N10. With rewarming the latencies returned to normal at the end of the procedure. In one patient, transient cessation of pump flow for 2 mins led to abolition of N20 which subsequently returned with re-establishment of flow. All patients recovered satisfactorily with no neurological deficits.

Discussion

Our study demonstrated that hypothermia below temperature of 35°C causes progressive increase in latency of all three peaks. Both C_7 and cortex latencies increased in excess of the Erb's peak latency, suggesting a difference in sensitivity of central conduction from peripheral conduction to low temperature. This difference is further substantiated by the opposing trend in the change of amplitude with decrease in body temperature. The physiological basis for these differences is not clear. This study also demonstrated that it is feasible to monitor SSEP during hypothermic cardiopulmonary bypass, but that the influence of temperature must be taken into consideration in the interpretation of both latency and amplitude changes. We noted that the SSEP was resilient to changes in blood pressure down to 25-30 mmHg and there was no apparent change unless flow was actually interrupted. Although this is a non-invasive monitor, because of its relative insensitivity to changes in perfusion pressure, the value of intraoperative monitoring of SSEP during cardiopulmonary bypass must remain to be established.

Reference

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	Erb's pt LAT (msec)	(N10) AMP μV)	C_7 LAT	(N13) AMP	Cortex LAT	(N20) AMP	Erb's Cortex (msec)	C_7-Cortex (msec)
36	11.2 ±0.3	2.6 ±0.3	14.8 ±0.4	2.2 ±0.2	21.0 ±0.5	2.3 ±0.5	9.8	6.2
35	11.5 ±0.4	2.6 ±0.4	15.2 ±0.4	2.0 ±0.2	21.6 ±0.4	2.2 ±0.5	10.1	6.4
34	11.8 ±0.4	2.8 ±0.3	15.7 ±0.4	1.9 ±0.2	22.6 ±0.5	2.1 ±0.5	10.8	7.0
33	12.3 ±0.4	2.8 ±0.3	16.3 ±0.5	1.8 ±0.1	23.9 ±0.6	1.9 ±0.5	11.7	7.7
32	12.6 ±0.4	3.0 ±0.3	16.9 ±0.5	1.7 ±0.1	25.2 ±0.8	1.7 ±0.4	12.6	8.3
31	12.9 ±0.4	3.2 ±0.3	17.6 ±0.5	1.5 ±0.2	26.3 ±0.7	1.6 ±0.4	13.4	8.7
30	13.4 ±0.5	3.5 ±0.3	18.3 ±0.5	1.4 ±0.2	27.4 ±0.8	1.1 ±0.4	14.0	9.2

Title: PROTAMINE, WHITE CELLS, PLATELETS AND EICOSANOIDS:
DOES PULMONARY HYPERTENSION MAKE A DIFFERENCE?

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Introduction. Heparin-protamine interaction results in a cascade of cellular and chemical events usually without concomitant hemodynamic changes. A recent report suggests that administration of protamine to patients with pulmonary hypertension (PHTN) may result in intense pulmonary vasoconstriction and cardiovascular collapse (1). The present study compared the effects of protamine-heparin interaction on white cells, platelets and selected eicosanoids (thromboxane A_2, prostacyclin) in patients with PHTN or normal pulmonary arterial pressures (NPAP).

Methods. Twelve (N=12) patients undergoing cardiac surgery utilizing cardiopulmonary bypass (CPB) were evaluated by a protocol approved by the Committee on Human Investigation. Patients were placed into Group I (I) PAP systolic 30 and mean 20 mmHg or Group II (II) PAP systolic 26 and PAP mean 16 mmHg based on preoperative measurement. Anesthetic management included fentanyl (75 mcg/kg), oxygen, and pancuronium in each case. Heparin anticoagulation maintained the activated clotting time (ACT) 400 seconds measured with the Hemochron(R). After CPB the patients were stabilized for 10 min and hemodynamic measurements were obtained at baseline and every 2.5 min during protamine infusion. Protamine (IV) was infused at (0.3 mg/kg/min) for a total dose equal to the heparin dose in mg. Samples drawn via arterial (A) and PA catheters at the start of infusion, 5 min later and 5 min after termination of infusion were analyzed for white blood count (WBC), differential white count (DWBC) and platelet count (PLT) by phase contrast microscopy (corrected for hemodilution during the study period). Radioimmunoassays for platelet factor 4 (PF_4), prostacyclin as 6-keto-PGF_{1a} (6-PGF), and thromboxane A_2 as thromboxane B_2 (TXB) were performed on each sample. Transpulmonary gradients (A-PA) were calculated. Results are expressed as mean ± SEM. Data was analyzed by ANOVA and Student's t-test for paired and unpaired data (P 0.05 was considered significant).

Result. (Table I and II). The preop MPAP I: 38 ± 4 mmHg vs II: 16 ± 1 mmHg was different (P 0.004). The CPB duration for I (113 ± 15 min) and II (86 ± 8 min) were similar (P=NS). The total doses of protamine for I and II were 395 ± 23 vs 350 ± 50 mg (P=NS). PF_4 gradient changed significantly during the infusion period in group II only. Positive gradients indicate platelet release of PF_4 across the pulmonary circulation. No significant changes in WBC, PLT or eicosanoids was noted in either group during the study period.

Discussion. Biochemical, hematologic and hemodynamic changes associated with protamine neutralization of heparin were studied in the setting of normal or PAP. Platelet activation, evaluated by release of PF_4, occurs across the pulmonary circulation during infusion of protamine sulfate in patients without preoperative PHTN (Group II). PF_4 is a secretory product stored in platelet alpha granules and released during platelet activation. This is often but not always associated with with platelet aggregation. Significant aggregation of platelets was not noted. PF_4 gradients in Group I were positive throughout the measurement period but did not change during protamine infusion (P=NS). WBC and DWBC data revealed no pulmonary sequestration of white cells. The measurements of thromboxane A_2 and prostacyclin levels did not change during the protamine infusion. Activated platelets are the most frequent source of the vasoconstrictor thromboxane A_2. The infusion of protamine over 15-20 minutes was not associated with aggregation and sequestration of white cells or platelets. If aggregation of formed blood elements is a necessary intermediate for pulmonary vasoconstriction, slow protamine infusion is advantageous. The study design did not reveal any instances of adverse response indicative of pulmonary vasoconstriction and defines only the typical response to protamine. Effects of protamine neutralization of heparin on WBC, platelets and selected eicosanoids were not different in patients with PHTN under the conditions of this study.

Reference.

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TABLE I

Platelet and white cell changes during protamine infusion (mean ± SEM)

		Baseline	Infusion +5 (min)	End Infusion +5 (min)
WBC I ($10^3/mm^3$)	A	16.1 ± 1.5	15.4 ± 2.2	19.7 ± 2.7
	A-P	-1.4 ± 1.3	-0.9 ± 0.7	-1.5 ± 0.6
II	A	13.8 ± 4.3	10.9 ± 2.9	12.4 ± 4.3
	A-P	0.8 ± 0.5	0.8 ± 1.2	1.4 ± 1.7
PLT I ($10^3/mm^3$)	A	112 ± 15	107 ± 10	105 ± 14
	A-P	14.9 ± 6.9	-13.9 ± 4.2	-7.1 ± 4.9
II	A	116 ± 14	97 ± 8	92 ± 12
	A-P	3.3 ± 11.1	-19.4 ± 23.4	6.8 ± 8.2
PF_4 I (ng/ml)	A	640 ± 199	534 ± 208	147 ± 136
	A-P	26.3 ± 38.7	44.0 ± 105.5	13.9 ± 21.1
II	A	639 ± 18	516 ± 117	75 ± 10(*)(**)
	A-P	-74.4 ± 60.5	154 ± 63.9(+)	16.9 ± 8.3

* P<001 compared to baseline
** P<.02 compared to infusion +5
+ P<.05 compared to baseline gradient

I - Group 1 N=7
II - Group 2 N=5
A = radial artery sample
P = pulmonary artery sample

TABLE II

Eicosanoid production during protamine infusion (mean ± SEM)

			Baseline	Infusion +5 (min)	End Infusion +5 (min)
6-Keto-PGF_{1a} (pg/ml)	I	A	462 ± 154	447 ± 143	406 ± 152
		A-P	-445 ± 446	328 ± 316	-121 ± 81
	II	A	225 ± 83	200 ± 71	131 ± 80
		A-P	-30 ± 25	-13.5 ± 15	-28 ± 7
TXB_2 (pg/ml)	I	A	1369 ± 391	1104 ± 375	893 ± 256
		A-P	-113 ± 249	-171 ± 93	-75 ± 78
	II	A	659 ± 164	2668 ± 2520	737 ± 562
		A-P	159 ± 66	200 ± 336	-64 ± 39

I - Group 1 N=4
II - Group 1 N=4

Title: VECURONIUM OR ATRACURIUM FOR RAPID SEQUENCE INTUBATION

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Introduction. Vecuronium (V) and atracurium (A), intermediate duration, nondepolarizing neuro muscular blocking agents, were evaluated to determine their effectiveness as relaxants for rapid sequence intubation. Most commonly used for this purpose is succinylcholine which has rapid onset and short duration, but may have undesirable side effects in patients with eye injuries or neurologic defects. A rapid-acting, nondepolarizing drug may then be preferable. Large doses of pancuronium provide adequate intubating conditions within 75 sec, but may be associated with prolonged paralysis and tachycardia.[1] The use of priming doses for these agents has been suggested.[2] However, an initial subclinical dose of the nondepolarizing relaxant may lead to symptomatic muscular weakness and the inconvenience of a 5 min delay before injection of the remainder of the dose. The purpose of this study was to determine whether bolus doses of A and V could facilitate smooth intubation as rapidly as does succinylcholine.

Methods. This investigation was approved by the Institutional Review Board. Pilot data indicated that A in the dosage range of 1.5 mg/kg and V at 0.25 mg/kg were necessary for rapid paralysis without serious side effects. Nineteen patients in the A group and 15 patients in the V group were studied. All patients were ASA Class I or II without neuromuscular, renal or hepatic disease and were undergoing elective surgery. Ages ranged from 16-80 years and weight from 56-118 kg. The V group's neuromuscular function was assessed using the isometric twitch tension of the abductor pollicis muscle in response to ulnar nerve stimulation at the wrist. A Bard Biomedical peripheral nerve stimulator at a frequency of 1 Hz was used and force was quantified by a Grass FT-10 transducer and recorded. Preinduction monitoring was established and included automated blood pressure measurements. Anesthesia was induced by thiopentothal 3-5 mg/kg IV followed immediately by the injection of an IV bolus of either A 1.5 mg/kg or V 0.25 mg/kg. Exactly 60 sec after the injection of relaxant, the trachea was intubated. The overall intubation conditions were ranked as 3 - excellent: jaw relaxed, vocal cords open, no bucking; 2 - satisfactory: jaw relaxed, slight movement of cords, and no bucking; 1 - fair: less favorable, but intubation possible; 0 - impossible to intubate trachea due to inadequate muscle relaxation. The surgical procedure sometimes required change of the patients' position such that tension readings were impossible. Thus the duration of the neuromuscular block was defined as the interval to the return of 2 twitches in a visual train-of-four.

Results. Results are expressed as mean ± SE and intergroup comparisons utilized an unpaired t test. Intubation at 60 sec from the injection of relaxant was achieved under good conditions in all patients, with no difference between A and V groups (Table). Seven A patients developed significant hypotension (systolic decreases ranged from 28-42% below immediate preinduction levels within the first 60 sec). Three responded to intubation with immediate return to preinduction blood pressure levels or higher. The 4 remaining were given mephentermine (7.5 mg), with prompt restoration of blood pressure. The duration of neuromuscular block (as evidenced by the return of 1-2 twitches in a train-of-four) was not significantly different between A and V groups. Seven V patients had no twitch at the time of intubation. In those V patients who did show a twitch response at intubation, the mean percent twitch depression was 58 ± 10%.

Discussion. Relaxation permitting easy intubation occurred in the absence of a complete neuromuscular block suggesting slower equilibration in limb muscles. Both A and V provided good conditions for intubating within 60 sec. A had a 37% incidence of significant hypotension, but this was easily treated. Large doses of A and V provided good conditions for rapid intubation without markedly prolonged paralysis. Although V had a longer duration (as defined here), this was not significantly different from the duration of A. The data suggest that a bolus dose of V may be preferable to A for rapid sequence induction and intubation when succinylcholine is not indicated.

References

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Table 1 - Rapid Intubation

	Atracurium (N = 19)		Vecuronium (N = 15)
Intubation Score*	3 - 58%		3 - 73%
	2 - 42%		2 - 27%
	1 - 0%		1 - 0%
Hypotension (28-42% decrease)	37%		0%
Treatment†	16%		
Duration of Action, min (clinical)§	67 ± 3	N.S.	85 ± 7

* = laryngoscopy score:
3 = excellent: jaw relaxed, VC open, no bucking
2 = satisfactory: jaw relaxed, slight movement VC, no bucking
1 = less favorable: intubation possible
† = 7.5 mg mephenteramine
§ = return of 2 twitches in train-of-four

Title: USE OF NEW ANESTHESIA CIRCUIT FOR REMOTE VENTILATION DURING MAGNETIC RESONANCE IMAGING

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Introduction. Pediatric patients may require anesthesia to provide immobility during magnetic resonance imaging (MRI). While in the MR imager the patient is 10-12 ft remote from the anesthesiologist and his equipment. Furthermore, electronic ventilators and monitors do not function properly and interfere with image quality. To solve these problems a simple non-metallic manual ventilatory system was devised to permit "remote" control of anesthesia and ventilation. This report describes a new anesthesia circuit and reports results of its use in animals and humans.

Methods. The system (Fig I) consists of i) a Laerdal® RBII self-inflating bag (L bag); ii) Laerdal® non-rebreathing lip valve iii) a 15 ft, 7/8 in. I.D. Aerosol® corrugated tube (A tube) iv) an O_2 supply tubing. Ventilation was accomplished by intermittent manual compression of the bag.

6 dogs were anesthetized, intubated and ventilated with a Harvard ventilator. Control blood gas analysis and hemodynamic measurements (BP, HR, PAP, RAP, CO, TPR, LV dp/dt) were obtained via appropriately placed catheters. The dogs then were disconnected from the ventilator and hand ventilated with the new system. To simulate clinical conditions the L bag was compressed to produce the same rate and chest expansion achieved with the Harvard ventilator. Each dog was hand ventilated for 3 hours while the length of the A tube was progressively increased as follows: 1) 10 feet for 30 min; 2) 30 ft for 30 mins 3) 50 ft for 1 and 2 hours. Hemodynamics and blood gas determinations were made at the end of each test period.

Compliance of the various tubes (10, 20, 30, 40, and 50 ft) was measured by connecting each to the inspiratory and expiratory outlets of a Siemens Servo 900C Ventilator whose RR was set at 15/min and V_I at maximum. Each breath was pressure limited (by presetting the working pressure) at either 10, 20, 30, 40, 50 or 60 cm H_2O. A tube compliance curve was plotted by noting the equilibrated V_E, (the volume change with each incremental pressure increase) and computing V_T.

Additional studies were made in 5 children (ages 2-16 yrs, weight 15-65 kg) anesthetized, intubated and ventilated manually with the new system (Fig 1). Ventilation was monitored by observation for adequate bilateral chest expansion, and by an esophageal stethoscope; adequate oxygenation was assured by flowing 100% O_2 (10 L/min) into the L bag. BP was measured with an aneroid manometer connected by long tubing so as to be outside the magnetic field. Cardiac function was monitored via esophageal stethoscope and telemetric ECG. After MRI was completed (1-2 hours) and before ventilation was discontinued a blood sample was drawn for analysis.

Results. Data from the animal studies are tabulated in Fig 2. These demonstrated the hemodynamic stability, adequate ventilation and oxygenation achieved. A progressive respiratory alkalosis resulted from over-ventilation during the 3 hour period. Similar data were noted in the children: systolic BP remained stable (105 ± 8 to 118 ± 8 torr) as did HR (112 ± 13 to 134 ± 12 beats/min). Arterial blood gas analysis revealed full oxygenation and respiratory alkalosis (pH 7.55 ± 0.035; $PaCo_2$ 24 ± 2 torr; PaO_2 204 ± 38 torr, bicarbonate 20.5 ± 0.5 mEq/L). Compliance of the A tube averaged 0.155 ml/cm H_2O/ft.

Results are expressed as mean ± SEM. Student's t test was employed to determine statistical significance ($P < 0.05$).

Discussion. This new L bag system served as a simple method to provide safe remote pulmonary ventilation (up to 50 ft). The method permitted administration of satisfactory anesthesia during MRI without compromising the function of that instrument.

Fig 1

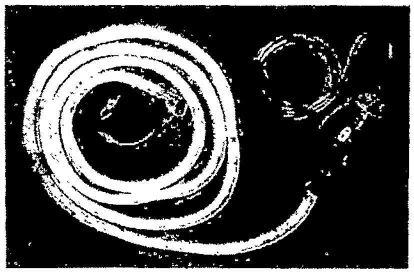
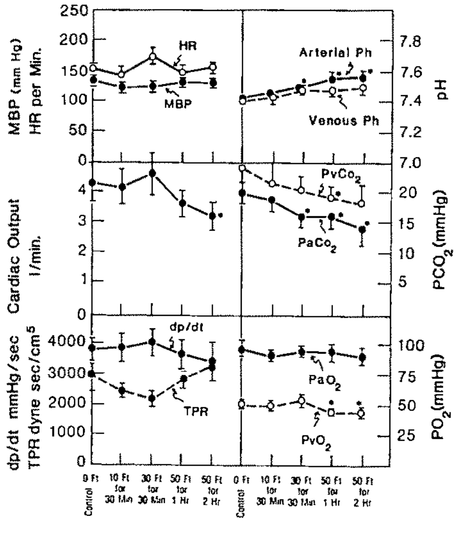


Fig 2



Footnote.

*P < 0.05 between control and each group.

Title: A CONTROLLED STUDY OF THE HEMODYNAMIC EFFECTS OF PROPOFOL VS THIOPENTAL DURING ANESTHESIA INDUCTION

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Introduction. This prospective study deals with Propofol, a new alkylphenol intravenous induction agent, and how it effects the systemic and pulmonary hemodynamics during induction of anesthesia as compared to a standard widely used agent, thiopental, in patients undergoing non-cardiac surgery.

Method. Forty adult (ASA Class II & III) patients, 22 females and 18 males (31-78 yrs, weight 32-114 kg) were entered into this study after giving their informed consent. The study was approved by the institution's committee on human research. All patients received meperidine 50-100 mg, pentobarbital 50-75 mg, and 0.4 mg atropine, intramuscularly 1 hour prior to arrival in the O.R. For monitoring, we used ECG surface electrodes (leads I, II, III and V-5), a blood pressure cuff and Doppler device, a triple lumen pulmonary artery flow-directed catheter (Edward Laboratory, Inc.) inserted through the right internal jugular vein into the pulmonary artery under local anesthesia, and a right radial artery cannula inserted percutaneously for direct blood pressure monitoring. Hemodynamic baseline measurements were taken before induction of anesthesia, 2-3 minutes post-induction and 5 minutes after intubation but before any surgical manipulation of the patient. With the patient breathing 100% oxygen by mask, induction of anesthesia was started by injecting a single bolus over 30-45 seconds of either propofol 2.5 mg/kg/IV or thiopental 5 mg/kg/IV in patients randomized into two groups. Oroendotracheal intubation was then accomplished using succinylcholine 1 mg/kg. Anesthesia was maintained with Isoflurane 0.5-2% and 50% N_2O in O_2 in a semi-closed circle system after the third set of data was obtained. Pancuronium was used, as needed, for muscle relaxation and reversed at the end of each case with neostigmine 1-2.5 mg and atropine 1 mg IV respectively.

Results. The demographic information is listed in Table I. There was no statistical sex, age or weight difference among the two groups. The mean induction dose of propofol was 193 mg and that of thiopental was 330 mg. Table II lists the mean hemodynamic parameters at pre-induction, 2-3 minutes post-induction, and 5 minutes post-induction before anesthesia maintenance and surgical stimulation. Significant reductions were observed with propofol: MAP (-23±12%), CI (-18±13%), LCWI (-35±16%), and LSWI (-35±18%) while thiopental produced lesser reductions: MAP (-5±12%), LCWI (-15±22%), and LSWI (-21±18%). Heart rate was increased by thiopental but was unchanged by propofol; CI was not significantly reduced by thiopental. Right sided cardiac parameters, PCWP, CVP, and MPAP were relatively unchanged by either agent. SVR and PVR were not significantly changed by either drug. These latter two indices are somewhat different from those reported by other investigators (1); who used an infusion technique rather than the technique employed by the present investigators.

Discussion. The reduction in mean arterial pressure, stroke index and left cardiac and ventricular work indices were significantly more decreased with propofol as compared to thiopental. The reduction in the left cardiac work indices in patients with impaired left ventricular function may, under some circumstances, lead to undesirable side effects; conversely these decreases insure less myocardial oxygen demand, a lower consumption of myocardial oxygen, a lower consumption of myocardial energy stores, and consequently greater preservation of functioning myocardium — a desirable goal in some circumstances. There were no pre- or post-induction complications and all surgeries were uneventful. There was one late surgical death which occurred twelve days post-operation due to disease and unrelated to the induction agent. Since the decreases in left sided heart parameters are much greater with propofol than with thiopental, extreme care must be exercised when using this new agent, especially in patients undergoing cardiac surgery, until further studies are performed to say differently.

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TABLE I PATIENT CHARACTERISTICS

DRUG	AGE	SEX	WEIGHT	HEIGHT	PHYSICAL STATUS	DOSE
DIPRIVAN	37-74 yrs $\bar{x}$ = 61 yrs	M = 10 F = 11	40-109 kg $\bar{x}$ = 65 kg	152-190 cm $\bar{x}$ = 168 cm	ASA II = 3 ASA III = 18	102-272 mg $\bar{x}$ = 193 mg
THIOPENTAL	31-78 yrs $\bar{x}$ = 52 yrs	M = 8 F = 11	32-114 kg $\bar{x}$ = 66 kg	142-185 cm $\bar{x}$ = 165 cm	ASA II = 7 ASA III = 12	160-570 mg $\bar{x}$ = 330 mg

TABLE II

HEMODYNAMIC PARAMETERS (MEAN ± SEM)

PARAMETERS		BASELINE	2-3 MIN POST-INDUCTION	5 MIN POST-INDUCTION and INTUBATION
HR bts/min	STP	88.70 ± 4.09	93.11 ± 3.83	102.05 ± 4.15*
	DIP	85.83 ± 3.17	84.43 ± 3.45	93.33 ± 3.63
MAP mmHg	STP	95.79 ± 3.39	91.42 ± 4.19+	93.89 ± 3.43
	DIP	101.60 ± 3.87	78.81 ± 4.24**	85.62 ± 3.78*
MPAP mmHg	STP	16.03 ± 1.36	18.05 ± 1.26	19.79 ± 2.02
	DIP	14.19 ± 1.19	14.71 ± 1.19	15.90 ± 1.35
PCWP mmHg	STP	9.31 ± 1.07	11.95 ± 1.20	12.26 ±1.22
	DIP	8.21 ± 1.11	9.10 ± 1.13	10.05 ± 1.27
CVP mmHg	STP	7.32 ± 0.88	9.47 ± 1.10	10.47 ± 1.21
	DIP	6.60 ± 0.83	8.29 ± 0.90	7.48 ± 0.89
CI L/M^2	STP	4.42 ± 0.22	3.96 ± 0.37	4.00 ± 0.26
	DIP	3.93 ± 0.17	3.24 ± 0.14*	3.65 ± 0.19
SI L/M^2	STP	51.01 ± 2.78	42.27 ± 2.97*	39.31 ± 2.13*
	DIP	46.53 ± 2.15	39.47 ± 2.09	41.09 ± 2.09
SVR dyne-sec.cm^5	STP	1660.79 ± 89.90+	1866.95 ± 183.42	1781.55 ± 127.79
	DIP	2006.96 ± 110.11	1781.05 ± 125.81	1617.25 ± 131.32
PVR dyne-sec-cm^5	STP	126.04 ± 17.22	149.07 ± 28.90	161.50 ± 25.20
	DIP	122.90 ± 14.57	143.23 ± 21.36	132.47 ± 18.53
LCWI g·m/M^2	STP	5.75 ± 0.37	4.86 ± 0.49+	5.09 ± 0.39
	DIP	5.39 ± 0.32	3.48 ± 0.25**	4.20 ± 0.26*
RCWI g·m/M^2	STP	0.95 ± 0.07	0.98 ± 0.16+	1.07 ± 0.14
	DIP	0.75 ± 0.07	0.65 ± 0.06	0.79 ± 0.08
LSWI ml/M^2	STP	66.86 ± 5.12	52.55 ± 4.64**	49.89 ± 3.25*
	DIP	63.42 ± 3.33	41.49 ± 2.26**	46.60 ± 2.54**
RSWI ml/M^2	STP	11.17 ± 1.27	10.45 ± 1.27	10.29 ± 1.08
	DIP	8.97 ± 0.84	7.75 ± 0.70	8.73 ± 0.86

STP = Thiopental
DIP = Diprivan

*p <.05, **p <.01 within drug
+p <.05, ++p <.01 between drugs

Title: COMPLEMENT ACTIVATION DURING SURGERY WITH AND WITHOUT CARDIOPULMONARY BYPASS

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Introduction. Activation of complement and the subsequent release of anaphylatoxins has been clearly demonstrated during cardiopulmonary bypass (CPB) (1). These anaphylatoxins, viz. C3a, C4a and C5a are biologically active peptides that mediate numerous inflammatory actions. An important study correlated clinical dysfunction after CPB with C3a concentration and forwarded the concepts of CPB having "damaging effects" and inducing a "whole-body inflammatory reaction" (2). Whether complement activation is a feature peculiar to CPB is unclear, since it may occur during thoracotomy without CPB (3). This study set out to re-evaluate this controversy by measuring the levels of C3a in a population of patients undergoing surgery with and without CPB.

Methods. This study was approved by the Institutional Research Committee. Informed consent was obtained. Twenty three male patients were studied. Nine underwent standard aorto-coronary bypass surgery with normothermic CPB and a bubble-type oxygenator (Group 1). Another 9 underwent thoracic vascular surgical procedures without CPB, such as descending thoracic aortic aneurysmectomy, coarctectomy etc., without the use of shunts (Group 2). An additional 5 patients undergoing thoracic surgery without the use of heparin and protamine, such as lobectomy, pneumonectomy etc., were also studied (Group 3). Blood samples were collected from either the patient arterial line or the CPB venous return line, where applicable, at the following intervals. In Group 1; baseline, post-heparin, CPB at 10, 20, 30 and 45 minutes, partial cross-clamp , post-protamine, arrival in ICU, and then at 3, 6, 12 and 24 hours post-arrival. In Group 2; as for Group 1, except that non-CPB post-aortic cross-clamp samples were collected at 10 minute intervals. In Group 3; samples were collected similarly for Group 2 , except that post-heparin and protamine samples were omitted. Concentrations of C3a were analysed in the samples by RIA. This entailed centrifugal separation of the plasma, addition to diNaEDTA and immediate freezing. C3a levels during CPB were corrected for pump prime hemodilution. Computer assisted statistical analysis of the data was performed using paired and unpaired t-tests.

Results. The results are demonstrated in Figure 1. In Group 1, C3a levels rose sharply during CPB, falling slightly during partial cross-clamp and the resumption of spontaneous cardiac activity, increasing again following protamine administration and then declining over the next 24 hours to normal levels. In Group 2, C3a levels remained within normal limits during surgery until protamine administration, whereupon they markedly increased. They then waned over the next 3-12 hours to normal levels. In Group 3, C3a levels were not elevated throughout the procedure and postoperative period. No significant difference ($p = 0.21$), was found between Group 2 and 3 during surgery until protamine administration. A comparison of Group 1 and 2 after protamine administration indicate that the C3a levels are significantly higher in the CPB group ($p < .01$), but decline at a slower rate following arrival in the ICU.

Discussion. The results for patients undergoing surgery with CPB are in general agreement with other studies (1,2). Of significance is the increase in C3a levels following protamine administration in both Group 1 and 2 patients, since it is known that protamine-heparin complexes are potent activators of the complement cascade (4). It is possible that these complexes in turn enhance and amplify complement activation during CPB. Furthermore, a complement mediated action has been implicated as one of the possible etiologic factors in protamine toxicity (5). In contrast, C3a is not generated in patients during thoracotomy without CPB or heparin/protamine. Further attention needs to be directed at studying the release of anaphylatoxins during protamine administration.

References.

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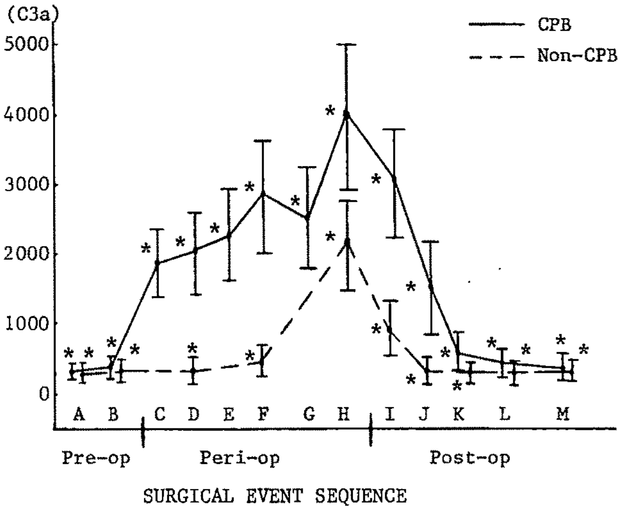
FIGURE 1. C3a LEVELS (ng/ml) DURING SURGERY WITH AND WITHOUT CARDIOPULMONARY BYPASS (* = $p < .01$)



A: baseline, B: post-heparin, C,D,E and F: q 10 mins during CPB, and q 5 mins post-aortic cross-clamp (non-CPB), G: partial cross-clamp, H: post-protamine, I: arrival in ICU, J,K,L and M: 3,6,12 and 24 hrs post-arrival.

Title: "DOSE RELATED CARDIOVASCULAR EFFECTS OF AMRINONE DURING ENFLURANE ANESTHESIA IN THE DOG"

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Introduction. Amrinone (A) is a cardiotonic drug with vasodilating activity distinct from digitalis glycosides and catecholamines. Single dose and short term oral and intravenous studies in unanesthetized subjects show dose-related improvements in cardiac index (CI), and left ventricular stroke work index, and substantial decreases in pulmonary artery mean pressure (PAM) and right atrial pressure (RA) with insignificant effects on mean arterial pressure (MAP) or heart rate (HR) (1). As patients may receive A in the perioperative period, a better understanding of its interactions with anesthetics is important. This study was designed to determine the dose related cardiovascular effects of A in the presence of the potent inhalation anesthetic enflurane (E).

Methods. Twelve mongrel dogs (22 ± 1 kg) with chronic tracheostomies were anesthetized with E (2.21 - 2.31% end tidal) in 40% O_2 in air. Normocarbia and normothermia were maintained. The end-tidal concentrations of E, CO_2, and O_2 were continuously measured by mass spectrometry. An arterial catheter was placed for direct blood pressure measurements and plasma sampling. A PA catheter was passed via an external jugular vein for measurements of thermodilution cardiac outputs (CO). A micromanometer tipped catheter was placed retrograde in the left ventricle via a femoral artery for direct left ventricular (LV) pressure measurement and electronic derivation of LV dP/dt. The plasma samples were analyzed for epinephrine (EPI), norepinephrine (NE), and A by HPLC. Systemic and pulmonary vascular resistance (SVR, PVR), CI, and stroke volume index (SVI) were calculated. The animals were divided into two groups of six dogs: an E-group which received only E, and an A-group. After 60 min of stabilization on the anesthetic, control measurements were made and plasma samples taken in both groups, which were repeated every 30 min in the E-group. In the A-group, each dog received the following sequential boluses and 30 min infusions: 1) the solvent alone; 2) A_1: 1 mg/kg+5 μg/kg/min; 3) A_2: 2 mg/kg + 10 μg/kg/min; and 4) A_3: 4 mg/kg + 20 μg/kg/min. Cardiovascular measurements and plasma samples were taken at 25 and 30 min after beginning each infusion in the A-group and also after 30 min of recovery following discontinuation of the A_3 infusion. Changes within each group were analyzed by analysis of variance for repeated measures with Bonferroni t-tests. A non-paired t-test was used to compare the results between the A-group and the E-group. A p value of less than 0.05 was considered significant.

Results. There were no significant effects from the solvent alone in the A group. There were no differences between the 25 and 30 min values for any variable during any of the infusions of A. Control (time 0) and 30 min values for MAP, PCWP, LV dP/dt, CI, SVR for the A and E-groups are given in the figure, along with 30 min plasma amrinone levels for the A-group. 2.21-2.31% end tidal E alone resulted in significant decreases in CI, SVI and LV dP/dt at 60, 90 and 120 min, without changes in HR, MAP, CVP or PCWP, compared to time 0. There was no difference between the A-group after 30 min of the A_1 infusion and the E-group at the comparable time. Significant differences from E after 30 min of A_2 included higher CI and LV dP/dt with lower SVR. Differences from E after 30 min of A_3, in addition to those effects, also included lower MAP, CVP, and PCWP. The differences in LV dP/dt and PCWP compared to E were still significant 30 min after the cessation of A_3 (time R). No significant differences were observed in HR, PAM, PVR, SVI, PR interval, EPI, or NE.

Discussion. The potent inhalational agents cause a dose-dependent depression of cardiac function. Boncyk et al, (2) anesthetized dogs with high concentrations of halothane (H) and found that very large doses of A were required to overcome the depressant effects of the high H on CO, doses which were associated with hypotension. This study has shown that the effects of A are dose-related in the presence of anesthetic concentrations of E. In contrast to other vasodilators, no reflex increase in plasma catecholamines was seen. Improvements in cardiac performance occurred at plasma levels of A below those at which significant decreases in MAP were seen.

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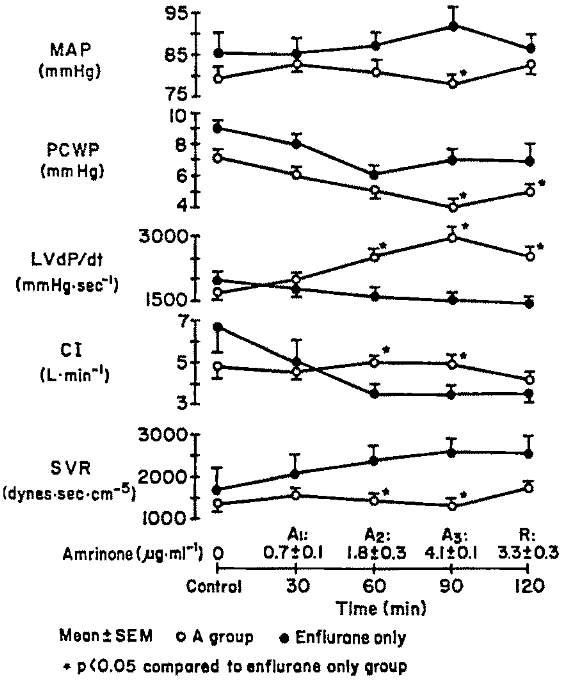

Title: OXYGEN-HEMOGLOBIN AFFINITY CHANGES DURING OPEN HEART SURGERY

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Introduction. It has been known from in vitro studies of red cell suspensions that the firmness of the hemoglobin-oxygen linkage is altered by changes in blood temperature, pH, 2,3-DPG and glucose concentration. More recently, hemodilution has also been claimed to affect O_2-hemoglobin affinity in patients undergoing surgery (1). Since hemodilution and hypothermia are routinely employed during the course of extracorporeal circulation, their effect on oxygen transport and delivery should be considered in open heart surgery. The partial pressure of oxygen at which 50% of hemoglobin is saturated (P50) was measured as the indicator of hemoglobin-oxygen affinity: a rise in P50 representing a right shift of the O_2 dissociation curve (ODC), enhancing oxygen delivery, and a fall in P50 or a left shift of the ODC causing an impediment to oxygen supply in the periphery.

Methods. Ten patients between the ages of 41 and 67 scheduled for aorto-coronary bypass surgery were studied. They were anesthetized with etomidate-fentanyl-pancuronium anesthesia and ventilated with N_2O/O_2 or O_2 by a Siemens-Elema ventilator. Extracorporeal circulation was carried out with a standard roller pump and a Travenol membrane oxygenator/heat exchanger primed with 2,000 ml of Ringer's lactate. P50 measurements were obtained from blood samples withdrawn via a self-guiding pulmonary artery catheter or at the venous inflow port of the oxygenator. Samples were taken immediately preceding skin incision, 5 min after commencing extracorporeal circulation at normothermia, 5 min after reaching a stable blood temperature of 26°C and 10 min after completion of the rewarming phase. P50 was determined at the respective blood temperatures by the Erythrox technique (2), a fully automated system which measures oxygen saturation electrophotometrically and plots an ODC within 15 min. In addition, the following hemodynamic and laboratory data were obtained: cardiac output, mean arterial blood pressure, hematocrit, arterial and venous pH and blood gases, blood glucose concentration and serum lactate. All institutional requirements regarding the study of human subjects were observed.

Results. Figure 1 shows the changes in P50 during the course of open heart surgery. The mean P50 control value for 10 patients before surgery was 24.9±1.6 mmHg, this value rose 9.5% after normothermic hemodilution and dropped 41.3% of control after hypothermia at 26°C. These changes were corrected for pH and are significant at the $p<0.02$ level. Following rewarming to 36.5°C, mean P50 returned to within 1.5% of the control value. Control hematocrit was 41.9±5.3% and dropped 24.6% after hemodilution. It regained 7.8% by the time of the fourth sampling. The mean blood glucose was 74.9±19.4 mg/dl and rose continually during the course of extracorporeal circulation to 108% over control, despite the fact that no glucose containing intravenous fluids had been administered. The control value of serum lactate was 11.5±4.4 mg/dl. This value rose 46.8% after hemodilution and reached 142.5% over control at the time of the fourth sampling. The main increase in lactate occurred between the third and the fourth sample.

Discussion. The volume of oxygen available to the tissues is not only dependent on the partial pressure gradient of O_2 but also on the affinity of hemoglobin for oxygen. An increase in P50 is advantageous to oxygen delivery since at any given pO_2, more oxygen is released to the tissues. Hypothermia, alkalosis, hyperglycemia and transfusion of banked blood, on the other hand, reduce the P50 and the oxygen availability to the tissues. A combination of these factors has been suspected to contribute to the condition commonly referred to as "rewarming shock". Our data suggest that this syndrome is unlikely to occur as a result of an increase in the hemoglobin-oxygen affinity at moderate levels of hypothermia. Some degree of protection, as yet poorly explained, may be afforded by hemodilution, while administration of banked blood is detrimental due to the low content of 2,3-DPG and other organic phosphates. In response to an equal temperature drop, we found a smaller ODC shift in blood cooled in vivo if compared to red cell suspensions cooled in vitro. This finding suggests that there are factors present during clinical hypothermia which modify the steep fall in P50 and tend to protect the patient against an impairment of oxygen delivery.

This work was supported in part by a grant of the US/German Fulbright Commission.

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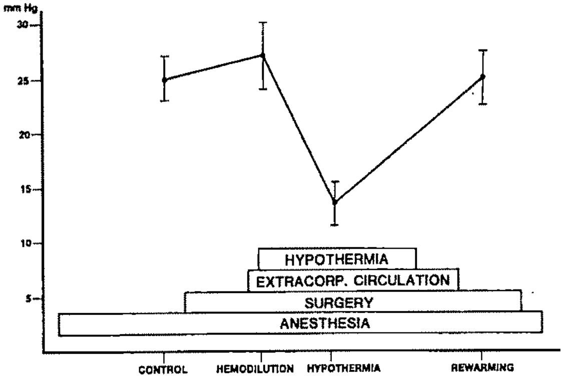

Fig. 1. P50 changes during open heart surgery (Mean of 10 patients ± SD)

Title: REGIONAL AND GLOBAL MYOCARDIAL METABOLIC AND CORONARY HEMODYNAMIC EFFECTS OF HALOTHANE IN CARDIAC PATIENTS DURING HIGH DOSE SUFENTANIL ANESTHESIA

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Introduction: Halothane has been reported to depress ventricular function and myocardial metabolism in patients with coronary artery disease (CAD), yet the extent to which it alters coronary circulation is still controversial.[1,2] This controversy has resulted in part because the response to halothane appears to depend on the drug's concentration, the duration of its administration, and the presence of other anesthetic drugs. Furthermore, the effects of halothane on regional and global myocardial metabolism and coronary hemodynamics during high dose sufentanil anesthesia is not known. The present study was, therefore, undertaken to evaluate the changes in global and regional myocardial blood flow and metabolism caused by halothane when administered as an adjunct anesthetic in cardiac surgical patients undergoing coronary artery revascularization under sufentanil anesthesia.

Methods: Eight patients scheduled for coronary artery bypass grafting (CABG) were included in the study with their informed consent. All patients were on calcium entry blockers, beta blockers and nitrates and were maintained on their medication until the day of surgery. Preanesthetic medication consisted of morphine sulfate (0.1 mg.kg^{-1}), scopolamine (0.4 mg) given intramuscularly, and oral lorazepam (1-2 mg). An additional 1-2 mg of lorazepam were given I.V. when needed during insertion of the catheters. A Baim coronary sinus (CS) catheter and a triple lumen pulmonary artery catheter were inserted via the right internal jugular vein under fluroscopy to ensure appropriate positioning. Additional monitoring included radial arterial line and two lead ECG (II and V4). Systemic arterial (SAP), pulmonary arterial (PAP), pulmonary capillary wedge (PCWP) and right atrial (RAP) pressures (mm Hg) and heart rate (HR) were recorded throughout the study. Cardiac output (CO, l.min^{-1}), coronary sinus blood flow (CSF, ml.min^{-1}) and great cardiac vein flow (GCVF, ml.min^{-1}) were measured by the thermodilution method. Stroke volume (SV, ml.b^{-1}) systemic (SVR) and pulmonary (PVR) vascular resistances (dyn.sec.cm^{-5}), global and regional myocardial oxygen consumption (CS-MVO2, GCV-MVO2, ml.min^{-1}) and lactate extraction (MLE) were calculated by the standard formulae. Blood samples for lactate and O2 content were withdrawn from the CS, GCV and arterial sites. Hemodynamic measurements and blood samples were obtained prior to (control) and during 1% halothane administration (15 min with H). The patients were given sufentanil (10-20 mcg.kg^{-1}) and metocurine (0.3 mg.kg^{-1}) for induction of anesthesia and muscle relaxation respectively. Halothane was administered following sternotomy in those patients who experienced an increase in SAP of more than 15% of pre-incision values. No attempt was made to interrupt the surgical procedure during the study since we were evaluating the effects of H under clinical conditions. Data were analyzed with Student's t-test.

Results: The data are presented in the Table. The decrease in mean SAP by 21% ($p < 0.001$) was primarily due to a decrease (13%) in SVR ($p < 0.05$) and SV (16%, $p < 0.05$). Both left (PCWP) and right (RAP) ventricular filling pressures decreased during halothane administration by 19% ($p < 0.02$) and 15% ($p < 0.05$) respectively. At the same time CSF did not change significantly (6%), while GCVF declined by 14% ($p < 0.05$). CS-MVO2(18%) and GCV-MVO2(23%) decreased with halothane. Myocardial lactate was released into the GCV but not in the CS, in one patient during halothane administration.

Discussion: It has been recently reported that H caused significant reduction in global MVO2 in CAD patients almost entirely due to a decreased oxygen extraction,[2] rather than to a decreased CSF. In another study, also in CAD patients, H was found to produce a significant decrease in global MVO2, in MO2 extraction as well as a significant decrease in CSF. In these studies H did not induce any release of lactate in the CS. In our study we observed a decrease in CS-MVO2 and also in GCV-MVO2, yet only GCVF decreased. Furthermore in one of our patients lactate release was detected in the GCV blood sample but not in that from the CS. These changes were attributed to the significant reduction of the SAP with H.

It is therefore concluded that although halothane appears to preserve global myocardial metabolism and oxygenation despite its systemic hemodynamic effects, regional myocardial hypoperfusion in patients with CAD may occur leading to local anaerobic glycolysis and lactate release.

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Table
(Mean ± SEM, n=8)

	Prior to H	With 1% H
HR	55 ± 4	57 ± 5
SAPm	96 ± 5	77 ± 3****
PAPm	14 ± .5	11 ± .5***
PCWPm	9.5 ± .3	7.7 ± .4**
CO	4.28 ± .3	3.73 ± .3*
SV	79 ± 5	66 ± 4*
SVR	1,806 ± 16	1,585 ± 113*
CSF	109 ± 10	103 ± 11 nc
GCVF	58 ± 8	50 ± 7*
MVO$_2$ CS	10.3 ± 1.3	8.4 ± 1.0*
MVO$_2$ GCV	6.1 ± 1.0	4.7 ± 0.6*

* $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$; **** $p < 0.001$

Title: PHARMACOKINETICS OF SUFENTANIL IN THE ELDERLY

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Introduction. It is well established that physiological changes accompanying advanced age can alter the distribution and elimination of narcotics (1-5). This study was designed to determine the pharmacokinetics of sufentanil, a new synthetic opiate, in elderly surgical patients.

Methods. Five elderly patients (ages 71-80) and five younger patients (ages 22-57) scheduled to undergo laminectomy, transphenoidal hypophysectomy or carotid endarterectomy were included in the study after obtaining institutional approval and informed consent. All patients had normal liver function and no evidence of cardiac failure. Anesthesia was induced with thiopental and tracheal intubation was facilitated with succinylcholine. Anesthesia was maintained with $N_2O:O_2$ (60-40%), isoflurane 0.25-0.5% and a continuous infusion of vecuronium to obtain muscle relaxation. Following a bolus injection of sufentanil (2 ug/kg), heparinized arterial blood samples were obtained at 1, 3, 5, 10, 15, 20, 30, 45, 60 min and at half-hour intervals thereafter to 4 hrs. Plasma was separated and frozen until assayed by radioimmunoassay, sensitivity 0.1 ng/ml. At the termination of anesthesia, it was assessed whether patients required a narcotic antagonist (criteria for respiratory depression was $\leq$ 8/breaths/min).

Plasma concentration-time curves from each patient were fitted to both bi- and triexponential equations, using weighted, nonlinear least squares regression analysis. The best fit for the data was then determined using the method of Boxenbaum (6). Pharmacokinetic parameters were calculated by using a method for bolus iv injection of a drug. Comparisons between the pharmacokinetic parameters for the elderly and young patients were made by applying Student's t-test for unpaired data (two-tailed).

Results. Plasma decay curves for sufentanil in both groups are best described by a biexponential equation. The pharmacokinetic data for both groups are presented in Table 1. Plasma albumin concentrations for the two groups were not significantly different, 4.1 ± 0.5 g/dl (mean ± SD) in the young, and 3.7 ± 0.3 g/dl in the elderly. Four of the five elderly patients studied required a single dose of naloxone at the termination of anesthesia to reverse respiratory depression. None of the younger patients required a narcotic antagonist. All anesthetics were of similar duration (3-4 hr).

Discussion. The data demonstrate decreased plasma clearance and decreased initial volume of distribution in the elderly patients. These observations are most likely the result of decreased hepatic clearance of the drug in elderly patients, reflecting a reduced splanchnic blood flow with slow delivery of drug to the liver and decreased total body water respectively. Previous studies of the kinetics of narcotics in elderly patients have all demonstrated reduced drug clearance and a prolonged $t_{1/2}$ elimination (3-5). Stanski, studying morphine in 4 elderly patients, is the only one to demonstrate a reduced initial volume of distribution (3).

In this study, the absence of prolonged $t_{1/2}$ elimination phase in elderly patients receiving sufentanil reflects the fact that although the clearance rate is decreased, the total volume to be cleared is similarly depressed in these patients. The facts that we observed no difference in $t_{1/2}$ elimination between elderly and younger patients receiving sufentanil yet the majority of the elderly patients required a narcotic antagonist at the termination of surgery suggest that the initial concentration gradient between the plasma and brain may be important in determining the duration of action of sufentanil in elderly patients. Such a possibility is implied by Berkowitz, who noted initial serum levels of morphine were higher in patients over 50 yr than in younger patients, but that this difference in serum morphine concentration between the two groups had disappeared by 10 min (1).

Supported in part by a grant from Janssen Pharmaceutica.

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Table 1. Pharmacokinetic Parameters (Mean ± SD)

	Young, n=5 (22-57 yrs)	Elderly, n=5 (71-80 yrs)	P
$t_{1/2}$ elim (min)	141 ± 61	156 ± 99	NS
Clp ($ml \cdot kg^{-1} \cdot min^{-1}$)	21.0 ± 4.5	12.7 ± 3.6	<0.025
V_i ($ml \cdot kg^{-1}$)	517 ± 134	320 ± 104	<0.05
Vd_{area} ($ml \cdot kg^{-1}$)	4171 ± 1782	2548 ± 1073	NS

Title: REINFARCTION FOLLOWING ANESTHESIA AND CABG FOR POST-INFARCTION UNSTABLE ANGINA

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Introduction. Post-infarction unstable angina (PIUA) is a manifestation of continuing ischemia after an acute myocardial infarction (AMI). Aggressive medical therapy for PIUA has a reported mortality of 56% over six months[1]. Since risk of reinfarction following anesthesia and non-cardiac surgery is significantly higher when an AMI has occurred 0-6 months prior[2,3], concern is expressed that patients who have had a recent AMI complicated by PIUA may be at excessively high risk for coronary revascularization. This study was undertaken to determine the reinfarction and mortality rate in patients following anesthesia for coronary artery bypass grafts (CABG) 1 to 30 days after an AMI complicated by PIUA.

Methods. After institutional approval by our Human Studies Committee, we prospectively followed the outcome of 64 consecutive patients admitted to our coronary care unit with an AMI complicated by PIUA from January, 1982, to December, 1983. Each patient underwent coronary revascularization for persistent myocardial ischemia 1 to 30 days after an AMI. Each AMI was documented by clinical history, ECG changes and changes in cardiac enzyme determinations. Intra-aortic balloon pump was utilized perioperatively when deemed necessary. All patients had peripheral artery and pulmonary artery catheters inserted prior to induction of anesthesia. Systemic arterial and pulmonary artery pressures were monitered continuously, along with Leads II and V_5 on ECG. Pulmonary artery wedge pressure and cardiac output were monitored intermittently. Induction of anesthesia in all cases consisted of fentanyl, muscle relaxant, and O_2 or fentanyl, Valium, muscle relaxant, and O_2 after various premedications. Immediate measures were undertaken to control adverse hemodynamic changes at all times. Hemodynamic monitoring was continued after surgery. Each patient's ECG was closely monitored and suspcious ECG changes were evaluated by determination of cardiac enzymes. Perioperative reinfarction was diagnosed by a cardiologist based on clinical history, ECG changes and appropriate changes in cardiac isoenzymes.

Results. The reinfarction rate for this group of patients was 6.3%. Mortality rate was 7.8% with five deaths occurring within 180 days postoperatively. Of the patients who reinfarcted (4), 50% died within 180 days.

Discussion. The reinfarction rate of 6.3% following anesthesia for coronary revascularization 1 to 30 days after an AMI compares well to a recently reported reinfarction rate for non-cardiac surgery[2]. That work reports a 5.7% reinfarction rate for patients undergoing anesthesia for non-cardiac surgery within three months after an AMI. The mortality rate of 7.8% following anesthesia for CABG is considerably better than that of medical management over a six-month period post-AMI. The results of this study suggest that patients with continuing myocardial ischemia after an AMI can undergo anesthesia for coronary revascularization within 30 days of the AMI with a significant but acceptable risk.

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Title: SAFETY AND EFFICACY OF OH 101 - MIXTURE OF EDROPHONIUM AND ATROPINE. A REVERSAL AGENT.

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Introduction. Edrophonium has gained popularity as an antagonist of non-depolarizing neuromuscular blocking drug because it has faster onset time and lower atropine requirement than neostigmine resulting in minimal changes in heart rate and blood pressure[1]. This study was to investigate the safety and efficacy of OH 101; a mixture of edrophonium chloride 10 mg/ml and atropine sulfate 0.014 mg/ml, in the reversal of pancuronium or atracurium induced neuromuscular blockade (NMB) under general anesthesia.

Methods. Fifty ASA I or II patients, ages 19-57 years and weighing 45-90 kg undergoing elective surgical procedures were studied after informed consent. All patients were premedicated and anesthesia induced with fentanyl 1-2 g/kg i.v., thiopental 4-5 mg/kg i.v. and maintained with 70% nitrous oxide in oxygen and either 1.25 MAC end tidal isoflurane (isoflurane) or supplemental doses of fentanyl and thiopental (balanced anesthesia) as required. The train of four (TOF) response of adductor pollicis muscle to supramaximal ulnar nerve stimulation was elicited and continuously recorded. Once a steady state of neuromuscular response was established patients were paralyzed with pancuronium 0.04 mg/kg or atracurium 0.2 mg/kg. Endotracheal intubation was performed at maximum NMB and ventilation controlled at a minute volume of 10-15 ml/kg. Further doses of pancuronium or atracurium were administered as required to maintain adequate surgical relaxation.

At the end of surgery, under controlled ventilation, and when at least two of the four responses of TOF were present, reversal was attempted with 0.05 ml/kg of OH 101 i.v. If TOF ratio >0.7 was not achieved in five minutes additional OH 101 was administered I.V. to a maximum dose of 0.12 ml/kg. Heart rate and rhythm were monitored and recorded continuously for two minutes prior to and ten minutes following administration of OH 101. Analysis was performed by Student's t-test and P<0.05 was significant.

Results. In 86% (43) of the patients TOF ratio >0.7 was achieved in 5 mins following a single dose of OH 101. 14% (7) of the patients received a second dose of OH 101 to achieve a TOF ratio >0.7. Six of the seven patients requiring a second dose of OH 101 for adequate reversal had NMB induced with pancuronium. This was significantly different from those who had received atracurium for NMB but was not influenced by the type of anesthetic. The mean TOF ratio in all patients before and at 1, 2, 5, and 10 mins following administration of OH 101 is shown in Fig. 1. TOF ratio before and at 1, 2, 5, and 10 mins following OH 101 were significantly different in patients paralyzed with atracurium compared to pancuronium.

The mean heart rate was significantly higher in the patients anesthetized with isoflurane before and one minute following OH 101 compared to patients under balanced anesthesia. There was also a wide range of individual variation of heart rate ranging from -40 to +61% at one min following OH 101 and persisting throughout the observation period (Fig. 2). Nodal rhythm or bradycardia developed in twelve patients (24%) of which nine patients (18%) converted to sinus rhythm spontaneously. Three patients, all under balanced anesthesia, received an additional dose of atropine to treat bradycardia (<40).

Conclusion. Effective antagonism of atracurium or pancuronium induced neuromuscular blockade was achieved with OH 101. The dose of OH 101 may be dependent on the neuromuscular blocking drug and the background anesthetic used.

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Fig. 1. Train of four ratio following OH 101. *p<0.05.

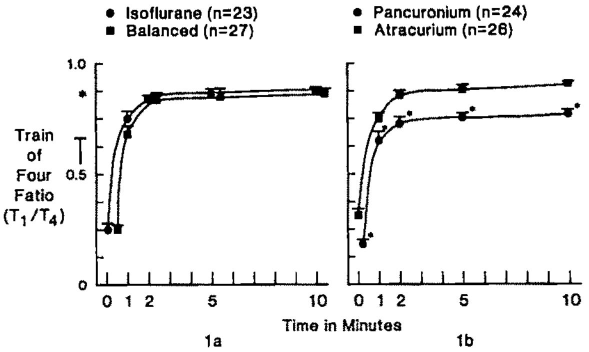
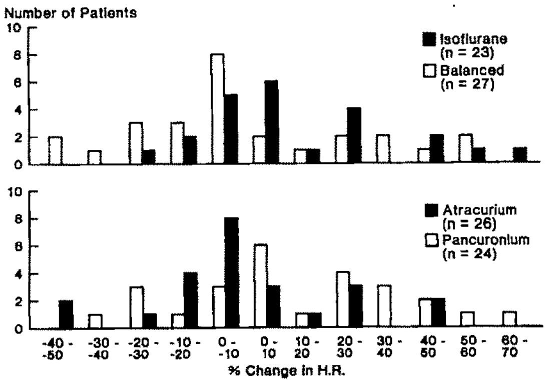


Fig. 2. Distribution of patients according to percent change in heart rate at one minute following OH 101.



Title: ACCELERATED ONSET OF PANCURONIUM, ATRACURIUM, AND VECURONIUM. A COMPARISON TO SUCCINYLCHOLINE.

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Introduction. The "priming principle" or the administration of non-depolarizing neuromuscular blocking drugs in divided doses have been shown to accelerate the onset of neuromuscular blockade (NMB)[1]. This study was designed to compare the rate of onset and degree of NMB following pancuronium (Pan), atracurium (Atr), and vecuronium (Vec), given either as a single bolus injection or in divided doses where a priming or subparalyzing dose is injected 3 or 5 min prior to the second or intubating dose and compared with succinylcholine (Sux).

Methods. 80 ASA I or II patients ranging in age from 18 to 60 years, undergoing elective surgery were studied. The study protocol was approved by the Human Research Review Board of the institution, and informed consent was obtained from each patient. Patients were premedicated with morphine 0.1 - 0.2 mg/kg i.m. and scopolamine 0.003-0.004 mg/kg i.m. 45-60 mins prior to induction of anesthesia. Anesthesia was induced with fentanyl 1-2 µg.kg i.v. and thiopental 4-5 mg/kg i.v., and maintained with 70% nitrous oxide in oxygen. Following an additional dose of 50 to 100 mg of thiopental, the larynx was sprayed with 4% lidocaine and the trachea was intubated. Anesthesia was maintained using 70% nitrous oxide in oxygen and incremental doses of 25-50 g of fentanyl, when necessary. The twitch response of the adductor pollicis muscle to ulnar nerve stimulation was elicited by supramaximal square wave pulses of 0.2 ms duration at 0.15 Hz and quantitated continuously by an FT-10 transducer. Once a baseline twitch response was established, the patients were assigned randomly to one of ten groups (N = 8) shown in Table 1. These doses were obtained from previously determined dose response curves of each drug. The dose of sux 1 mg/kg administered is typically used for endotracheal intubation in adults.

The following experimental parameters were measured 1) % suppression of the twitch after the priming dose, 2) % suppression of the twitch at 30, 60, and 90 sec and time to maximum suppression of the twitch response following the bolus or second dose, and 3) time for recovery of the twitch response from maximum blockade to 25% of control. Time to maximum NMB and time to 25% recovery were analyzed by both Student's paired t-test and analysis of variance. The degree of NMB at 30, 60, and 90 sec were analyzed by Student's t-test on ranked data. P<0.05 was considered statistically significant and values are Mean + S.E.M.

Results. % suppression of twitch following Sux, and bolus or divided doses of Pan, Atr, and Vec are shown in Fig. 1. The time to maximum NMB following Sux is significantly different from bolus and divided doses of Pan, Atr, and Vec. Also, the time to max NMB for divided doses of Pan, Atr, and Vec are significantly different from bolus dose of same drug. Time to 25% recovery of twitch were significantly different for each drug but there was no difference when they were administered as bolus or divided doses.

Conclusion. The results show that adequate degree of NMB to facilitate endotracheal intubation may be achieved with divided doses of non-depolarizing neuromuscular blocking drug in 60 to 90 secs. This regimen may be used to facilitate endotracheal intubation when Sux, a depolarizing neuromuscular drug, is contraindicated or when there is a desire to avoid its side effects.

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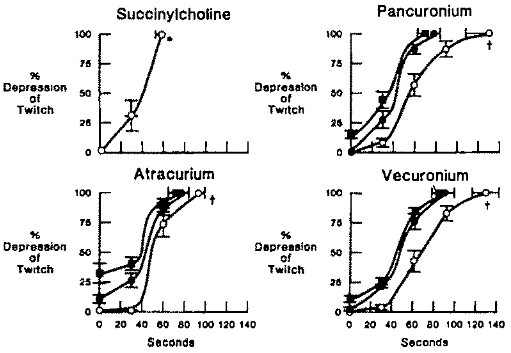
Table 1. Groups and drug dosage.

Groups	Drug	Priming dose (ED_{10}) (mg/kg)	Second dose ($2ED_{90}$) (mg/kg)	Bolus or Total dose* (mg/kg)	Time Interval (mins.)
I	Sux	-	-	1.0	None
II	Pan	-	-	0.095	None
III	Pan	0.015	0.08	0.095	3
IV	Pan	0.015	0.08	0.095	5
V	Atr	-	-	0.53	None
VI	Atr	0.07	0.46	0.53	3
VII	Atr	0.07	0.46	0.53	5
VIII	Vec	-	-	0.07	None
IX	Vec	0.01	0.06	0.07	3
X	Vec	0.01	0.06	0.07	5

*ED_{10} + $2ED_{90}$ except for Sux.

Fig. 1. The effect of administration of neuromuscular blocking agents as a bolus dose (o) or as divided doses with 3 min (●) or 5 min (■) between doses.



*p<0.05 Sux vs bolus or divided doses.
†p<0.05 divided doses vs bolus dose.

Title: DELAYED NIMODIPINE TREATMENT IMPROVES CEREBRAL BLOOD FLOW AFTER COMPLETE CEREBRAL ISCHEMIA IN DOGS

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Introduction. Following an insult of complete cerebral ischemia, there is a transient period of reactive hyperemia followed by a prolonged period of cerebral hypoperfusion which lasts 6-24 h. During this time the cerebral blood flow (CBF) may be inadequate to supply the nutrient and oxygen demands of the cells, thereby producing an insult of incomplete ischemia (1). Nimodipine, a calcium entry blocker with cerebrovascular specificity, can ameliorate this post-ischemic hypoperfusion and may improve neurologic recovery if given before or immediately after 10 min complete cerebral ischemia in dogs (2,3). However, immediate post-resuscitation treatment with nimodipine following complete cerebral ischemia from cardiac arrest may not be possible. The purpose of the present study was to determine whether delayed treatment with nimodipine might ameliorate or reverse the delayed hypoperfusion state. The effects of nimodipine, given 15, 30, or 60 min following complete cerebral ischemia, on cerebral blood flow and resistance (CVR) were measured in dogs.

Methods. Three groups of six dogs were anesthetized with 0.8% halothane, 70% N_2O, in O_2. Ventilation was controlled to maintain normocarbia. Cannulae were placed in the femoral artery and vein for blood sampling and pressure measurement and into the posterior sagittal sinus for measurement of CBF. Mean arterial pressure (MAP), intracranial pressure (ICP), temperature, electrocardiogram, and 4-lead electroencephalogram were monitored continuously. A right-sided thoracotomy was performed and umbilical tapes were placed around the ascending aorta and both venae cavae. After discontinuation of the halothane, pre-ischemic control measurements were taken. Complete cerebral ischemia lasting 10 min was achieved by simultaneously occluding the ascending aorta and venae cavae. Immediate resuscitation consisted of the administration of intravenous fluids and $NaHCO_3$. Dogs were then randomly assigned to one of three treatment groups. A bolus dose of nimodipine, 10 $\mu g \cdot kg^{-1}$, followed by a constant infusion at a rate of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was given at 15, 30, or 60 min post ischemia. Blood gases and chemistries, MAP, ICP, CBF, CVR, and $CMRO_2$ were measured for 120 min post-ischemia. Results were compared to an untreated group (1).

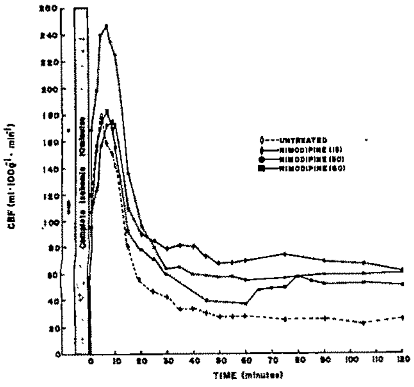

Fig 1: Cerebral blood flow following ischemia

Results. In all groups there was a transient increase in CBF followed by a decrease in CBF until treatment with nimodipine was instituted (Fig 1). In the groups treated at 15 and 30 min post-ischemia CBF remained above 60 $ml \cdot min^{-1} \cdot 100g^{-1}$. In the group treated at 60 min there was a progressive decline in CBF to 37 $ml \cdot min^{-1} \cdot 100g^{-1}$. CBF immediately increased to 48 $ml \cdot min^{-1} \cdot 100g^{-1}$ after the nimodipine bolus, and during the nimodipine infusion CBF continued to increase so that it was maintained above 50 $ml \cdot min^{-1} \cdot 100g^{-1}$ for the remainder of the study. In the nimodipine groups CBF was approximately double that of the untreated group. The changes in CBF reflected changes in CVR, in which a transient decrease in CVR was followed by increased CVR until treatment with nimodipine was initiated (Fig 2).

Discussion. This study demonstrates that nimodipine is capable of ameliorating or reversing the delayed post-ischemic hypoperfusion state. In this model of complete cerebral ischemia, restoration of blood flow is followed by a prolonged period of increased cerebrovascular resistance which severely limits CBF such that a state of incomplete ischemia may be produced. Delayed treatment with nimodipine at 15 and 30 min can prevent such severe hypoperfusion; and nimodipine treatment at 60 min can markedly decrease the CVR to improve CBF. Since this post-ischemic hypoperfusion state is believed to contribute to the ultimate neurologic damage, treatment with nimodipine, even if delayed up to 60 min, may improve outcome.

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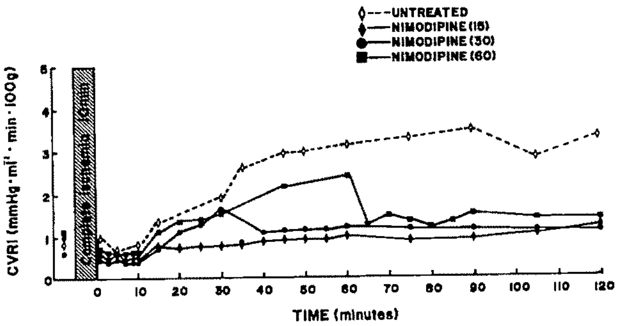

Fig 2: Cerebrovascular resistance following ischemia

Title: **THE CARDIOVASCULAR EFFECTS OF FENTANYL REVERSAL BY NALOXONE AT VARYING ARTERIAL CO_2 TENSIONS IN DOGS**

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INTRODUCTION. Although intravenous narcotics may offer anesthesia with preservation of cardiovascular function and without production of stress-related hormones, post-operative hypoventilation with hypercapnia may be a problem. After naloxone reversal of narcosis, severe hemodynamic instability may ensue; arrhythmias, hypertension, pulmonary edema, and even deaths have been reported (1,2,3,4). In this study we investigated in the canine model the effect of arterial carbon dioxide tensions on the cardiovascular response to narcotic reversal.

METHODS. Six dogs each underwent three randomized experiments, no dog repeating sooner than two weeks. The dogs were induced with 10 mg/kg intravenous thiopental and intubated after 1 mg/kg succinylcholine. Enflurane (1,5% inspired) in oxygen was given by controlled ventilation throughout the experiment. Percutaneous venous and arterial cannulae were placed for drug administration, fluid replacement, and continuous blood pressure measurement and blood sampling. Periodic measurements included systolic, diastolic, and mean arterial pressures (BP), heart rate (HR), and plasma epinephrine (E) and norepinephrine (NE) levels as determined by high performance liquid chromatography. After a control sample, 50 mcg/kg fentanyl (F) was given over 5 minutes and measurements were done 5 and 45 minutes later, for all dogs. Ventilation was then changed to produce an arterial CO_2 tension of 20 torr (Group 1), 35 torr (Group 2), or 60 torr (Group 3), and measurements were repeated. End-tidal CO_2 was followed by mass spectroscopy and confirmed by arterial blood gas determinations. After the ventilation change none of the unparalyzed dogs moved or attempted to breathe. Vecuronium (0.1 mg/kg) was given two minutes before naloxone (Nx), 0.4 mg, was injected and measurements were taken 1, 5, and 10 minutes thereafter. After restoring normocapnia, a further set of measurements was taken, and an additional 0.4 mg bolus of Nx was given followed by the final sample. After analysis of variance and appropriate t-tests, $P < 0.05$ was used for statistical significance.

RESULTS. The administration of F resulted in the prompt decrease in BP and HR ($P < .01$), which persisted over the next 45 minutes. Plasma E and NE levels were also significantly suppressed. Forty five minutes after F, Group 3 animals were hypoventilated to an arterial CO_2 of 65 torr, which caused a significant increase in HR, E, and NE levels. Group 1 dogs were hyperventilated to a CO_2 of 25 torr, which significantly increased HR. Group 3 dogs had significantly greater elevations in HR, E, and NE levels when compared with Groups 1 or 2 after the CO_2 change. Naloxone resulted in prompt and significant increases of HR and BP for all groups, which persisted for 10 minutes. One minute after Nx, BP was significantly higher in Group 3 compared with Group 1 (but not Group 2), and E was higher in Group 3 than either Group 1 or 2. In fact, significant changes in E following naloxone never occurred in Group 1. Restoring ventilation to normocapnia, and the second naloxone administration produced no statistically significant changes.

DISCUSSION. Naloxone reversal of F produced dramatic increases in the hormonal and cardiovascular parameters measured. The catecholamine changes occurred much more quickly (1 vs. 5 or 10 minutes) and mean BP was significantly higher in the hypercapnic compared with hypocapnic dogs. It appears from this study that the abrupt sympathetic cardiovascular response to narcotic reversal can be blunted if normo- or hypocapnia is established prior to naloxone administration.

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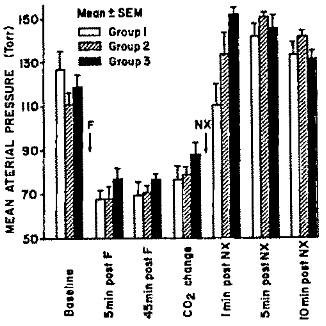

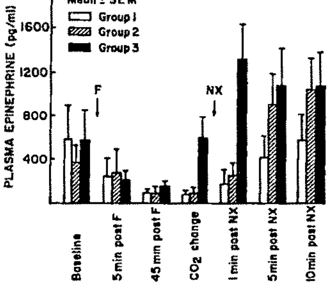

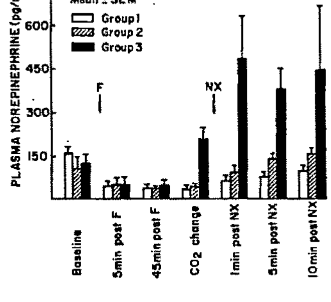

Title: EFFECT OF SUCCINYLCHOLINE ON SERUM POTASSIUM IN PATIENTS WITH BRAIN TUMORS

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Introduction. Hyperkalemia following succinylcholine has been described in a variety of upper motor neuron disorders (1-3). Two reports of succinylcholine-induced hyperkalemia without accompanying EKG changes (4,5) in patients with upper motor neuron pathology led us to investigate whether "transient acute silent hyperkalemia" occurred with any frequency in patients with brain tumors, either with or without evidence of motor nerve disturbances.

Methods. The study protocol was approved by the University Human Investigation Committee and informed consent was obtained. The subjects were 15 consecutive patients scheduled for elective craniotomy and tumor resection. Patients ranged in age from 44-75 years and were free of significant concurrent cardiopulmonary disease. Preoperative computed tomography (CT) scans revealed supratentorial tumors greater than or equal to 3 cm diameter in all patients. Nine of the 15 patients had hemiparesis or weakness of 2 days to 4 months duration prior to the day of surgery (Table 1). Peripheral cannulae for fluid and drug administration and a 20-gauge radial arterial catheter for blood pressure monitoring and blood sampling were placed using local anesthesia. EKG lead II was continuously monitored. General anesthesia was induced with thiopental 6 mg/kg IV and 70% nitrous oxide in oxygen. Ventilation was carefully controlled by mask to maintain a constant end-tidal CO_2 concentration verified by capnography. One minute before succinylcholine was given, an arterial blood sample was obtained for determination of baseline serum K+ level and blood gas tensions. One minute later, succinylcholine 1 mg/kg IV was administered over 5 sec. Repeat blood samples were obtained 1 and 10 min after succinylcholine and also were analyzed for serum K+ level and blood gas tensions. Changes in serum K+, arterial pCO_2, and pH were compared using Student's t-test for paired data. $P<0.05$ was regarded as significant.

Results. There was no statistically significant change in serum K+, arterial pCO_2, or arterial pH after succinylcholine (Table 2). The maximum individual increase in serum K+ was 0.4 mEq/l. No change in the ECG complex occurred following succinylcholine in any patient.

Discussion. The use of succinylcholine in patients with upper motor neuron pathology is controversial. The occurrence of hyperkalemia in patients with encephalitis (1), tetanus (2), ruptured cerebral aneurysms (3,4), and one patient with a brain tumor(5) has led many to conclude that succinylcholine should be avoided in all patients with CNS pathology. Conversely, this study and recent work in patients with cerebral palsy (6) indicate that succinylcholine may not be harmful, even in the presence of motor deficits. We deliberately measured serum K+ one minute after succinylcholine, a time when peak increases in K+ have been reported in patients with upper motor neuron lesions who became hyperkalemic after succinylcholine (4). In conclusion, we found no evidence to support the contention that succinylcholine might cause hyperkalemia in patients with brain tumors; we believe that when use of succinylcholine is indicated in such patients, it should not be withheld.

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Table 1. Preoperative Neurological Status and Awake Intracranial Pressure (ICP) in 15 Patients With Brain Tumors

Patient	Neurological Status	ICP (mmHg)
1	Normal	10
2	1 week left-sided weakness	10
3	Normal	15
4	Normal	15
5	4 months mild left-sided weakness	20
6	1 week left hemiparesis	15
7	1 month right hemiparesis	17
8	2 days right hemiparesis	17
9	Normal	15
10	Normal	15
11	3 weeks right-sided weakness	15
12	Normal	12
13	1 month left hemiparesis	15
14	2 weeks left hemiparesis	25
15	1 month left hemiparesis	10

Table 2. Serum Potassium (K+), Arterial pCO_2 and pH Before and After Succinylcholine (Sch) 1 mg/kg in 15 Patients with Brain Tumors

	1 Minute Before Sch	1 Minute After Sch	10 Minutes After Sch
K+ (mEq/L)	3.5±0.1	3.5±0.1	3.5±0.1
$PaCO_2$	37.7±1.4	38.0±1.4	38.0±1.9
pH	7.43±0.01	7.43±0.01	7.42±0.01

All values mean ± SE; No significant differences ($p<0.05$) occurred in any of the values measured following succinylcholine.

Title: VECURONIUM AND INTRACRANIAL PRESSURE IN MAN

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Introduction. The ideal agent for neuromuscular blockade in patients with reduced intracranial compliance should have minimal impact on both intracranial pressure (ICP) and systemic hemodynamics. Vecuronium is known to possess little hemodynamic effect (1) and a recent animal model has demonstrated no effect on ICP when intracranial compliance was artificially impaired (2). In order to determine whether these findings apply to humans, we have investigated the effect of vecuronium on ICP in patients with brain tumors.

Methods. The study protocol was approved by the University's Human Investigation Committee and informed consent was obtained. The subjects were 10 consecutive patients scheduled for elective craniotomy and tumor resection. Patients ranged in age from 47-75 years and were free of significant concurrent cardiopulmonary disease. Preoperative computerized tomography scans revealed supratentorial tumors greater than or equal to 3 cm diameter in all patients. Peripheral venous cannulae, a 20-gauge radial arterial catheter and a subarachnoid pressure bolt were placed under local anesthesia. Radial arterial and intracranial pressures were continuously transduced and recorded (Brush Model 440 recorder) with the zero reference point at the external auditory meatus. While the patients were awake, the intracranial volume-pressure relationship was assessed by injection of 1 ml of mock CSF through the pressure screw while the corresponding change in ICP was recorded. Anesthesia was then induced with thiopental, 6 mg/kg IV, and endotracheal intubation was performed after additional thiopental, 4 mg/kg IV, and succinylcholine, 1 mg/kg IV. Anesthesia was maintained with 70% N_2O in O_2 and ventilation was controlled to maintain end-tidal CO_2 tension at control values. Arterial blood gas samples drawn 2 minutes before and after vecuronium verified constant alveolar ventilation during the study. Recording of neuromuscular function was begun immediately after the initial dose of thiopental. Monitoring was performed with a force-displacement transducer measuring adductor pollicis twitch height in response to supramaximal ulnar nerve stimulation at 0.15 Hz delivered for a duration of 0.15 ms via 25-gauge subcutaneously placed needles. Following complete resolution of prior succinylcholine effect and a stable period of ICP and arterial pressure, vecuronium, 0.14 mg/kg IV, was administered as a bolus. Constant controlled ventilation was continued until 3 minutes after vecuronium administration. Sequential measured values for ICP and mean arterial pressure (MAP) were compared using one-way analysis of variance. Specifically, values obtained each minute after vecuronium were compared with both the awake control values and values obtained immediately before vecuronium administration. $P<0.05$ was considered significant.

Results. The patients studied are characterized in Table 1. All had computerized tomography findings that suggested the potential for abnormal compliance as evidenced by significant cerebral edema or a shift of midline structures. Eight patients manifested compromised compliance with VPR > 2 mmHg/ml. Six patients exhibited markedly abnormal compliance with VPR > 4 mmHg/ml. Study results are summarized in Figure 1. No statistically significant changes occurred in ICP or MAP after vecuronium, 0.14 mg/kg IV, was given. Arterial blood gas analysis before and after vecuronium confirmed constancy of ventilation and normocarbia (Table 1). Time to onset of 100% neuromuscular blockade following vecuronium was 107±34 seconds (mean±S.D.). In all cases, 100% blockade occurred prior to the end of the 3-minute study period.

Discussion. Whereas other muscle relaxants in widespread clinical use may have profound effects on ICP or systemic hemodynamics, we found that vecuronium, 0.14 mg/kg, has minimal effect on both ICP and MAP in patients with brain tumors. We conclude that vecuronium is a safe and effective neuromuscular blocking drug in patients with intracranial mass lesions.

Table 1

CT Appearance of Tumor			Intracranial Compliance	Arterial pCO_2(mmHg)	
Diameter(cm)	Midline Shift(mm)	Edema(0-3)*	ΔICP(mmHg/ml)	Before Vecuronium	After Vecuronium
4.2±0.4	7.5±1.9	2.1±0.2	4.1±0.6	38±2	38±2

All values = mean±SEM
*0 = no edema, 3 = edema throughout ipsilateral hemisphere

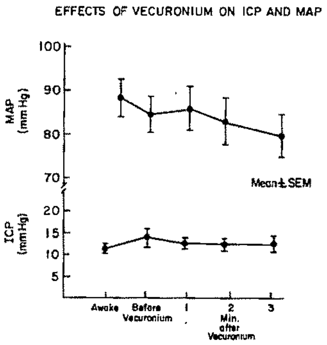

Figure 1

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Title: TRANSMUCOSAL NARCOTIC DELIVERY: AN EVALUATION OF FENTANYL (LOLLIPOP) PREMEDICATION IN MAN

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Introduction. Because of its high tissue solubility and potency, fentanyl may enable analgesia and sedation to be provided in a novel way, via topical administration. Fentanyl's stability, resistance to heat and solubility in candy matricies suggest that it could also be incorporated into a non-threatening, psychologically appealing delivery system, a candy lollipop. The purpose of this study was to evaluate fentanyl lollipop premedication in 28 adult human volunteers in terms of onset, duration and magnitude of analgesia and sedation, respiratory and circulatory changes, plasma fentanyl concentrations and side effects.

Methods. Approval was received from the FDA and the institutional human research board and permission obtained from 28 volunteers, 25-35 yrs old and 53-91 kg. The lollipops were made by heating a candy base to 150°C and adding 5 mg (n=7), 4 mg (n=3), 2 mg (n=8), 1 mg (n=2) and 0.5 mg (n=8) of fentanyl citrate crystals when the base cooled to 121°C. Following this the candy-fentanyl mixture was poured into molds at 107°C, a stick added and the lollipops allowed to cool and harden before removal from the molds. The volunteers had an IV infusion, continous Nellcor pulse oximetry, a standard blood pressure cuff and breathed room air. A Tursky (graded, electric pain delivering) electrode was attached to a forearm. Following this baseline systolic blood pressure (SBP), heart rate (HR), oxygen saturation, respiratory rate (RR) and end-tidal CO$_2$ (PETCO$_2$) were obtained and pain threshold measured using the Tursky electrode. After this, volunteers were given a lollipop and instructed to suck as fast (FS; n=20) or slow (SS; n=8) as comfortably possible. Repeat measurements of all variables were made at 10 min intervals and venous blood samples (5 ml) obtained for fentanyl assay every 20 min for the first hr, every 30 min for the second hr and hourly thereafter for 8 hrs. When the volunteers' oxygen saturation became lower than 80%, they were instructed to take a deep breath. Volunteers were asked to indicate when they first "felt different" and were questioned every 15 min to determine if they experienced nausea, pruritus, a headache or any other problem. Volunteers having one or more episodes of desaturation (O$_2$ sat < 80%) while sleeping or comfortably resting during the last hour of the experiment were given naloxone 0.4 mg, IV, in divided increments. Data were analyzed for statistical significance using analysis of variance, chi-square and t-test with Bonferroni correction factor.

Results. Consumption of the lollipops was significantly faster with fast suction (FS) 6.0 ± 1.8 min than slow or passive suction (SS) 44 ± 16 min and resulted in a faster onset of subjective changes (pleasant sleepy feeling) 7.7 ± 3.2 vs 22.1 ± 5.3 min. Onset of significant analgesia (defined as a 20% or greater increase in pain threshold) was similar (20-30 min) with all doses of lollipops but occurred faster (18 ± 8 vs 36 ± 13 min) with FS than SS. Many volunteers with high dose (4 and 5 mg) lollipops experienced marked degrees of analgesia (maximal safe current) and some would have tolerated electric currents which may have destroyed tissue. It was not always possible to precisely determine time of peak analgesic action but it appeared to be more closely related to speed of suction (20-35 min with FS vs 55-70 min with SS) than dose of fentanyl. Analgesia often lasted up to 8 hours with 4 and 5 mg lollipops but was only apparent for 60-100 min with 0.5 and 1.0 mg lollipops. PETCO$_2$ became and remained significantly elevated (10% > baseline) and respiratory rate significantly decreased (10% < baseline) at approximately the same time patients became analgesic. However, RR was not significantly changed at any time in volunteers getting 0.5 and 1.0 mg lollipops. PETCO$_2$ became elevated sooner and remained elevated longer with higher doses of fentanyl (4 and 5 mg) and FS than lower doses (0.5 and 1.0) and SS. Peak PETCO$_2$ values (52 ± 3 torr) were similar irrespective of rate of suction or dose of fentanyl after 2, 4 and 5 mg lollipops but were significantly lower 41 ± 3 torr after 0.5 and 1.0 mg lollipops. Peak plasma fentanyl concentrations varied a great deal but were highest with higher dose lollipops and occurred sooner with FS (10-25 min) than SS (45-70 min). Plasma fentanyl reached values as high as 20-25 ng/ml with the high dose lollipops and ranged between 0.7 and 3.1 ng/ml after 8 hrs. Eighty-six, 67 and 20% of volunteers having 5, 4 and 2 mg lollipops, respectively, needed occasional reminders to "take a breath" because of a decrease in oxygen saturation and one was given naloxone at the end of the experiment. No volunteers receiving 0.5 and 1.0 mg lollipops experienced any desaturation. SBP and HR were not significantly altered irrespective of speed of suction or dose of fentanyl consumed. Side effects were limited to volunteers receiving 2, 4 and 5 mg lollipops and included nausea (61%), vomiting (11%) and headache (33%). Interestingly no subject experienced any rigidity and side effects were most noted at the end of the study when volunteers stood up.

Discussion. These data demonstrate that fentanyl impregnated lollipops result in rapid increases in plasma fentanyl with accompanying analgesia, respiratory depression and usual opioid side effects (except rigidity) with high doses. The results suggest that lollipops with 0.5 and 1.0 mg (5-15 µg/kg) of fentanyl produce significant analgesia and sedation for short periods (1-2 hrs) with no side effects and little respiratory depression and deserve further study for premedication. Higher doses seem to cause too much respiratory depression and other side effects to be considered for premedication.

Title: FACILITATION OF ENDOTRACHEAL INTUBATION WITH A PRIMING DOSE OF ATRACURIUM IN CHILDREN

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Introduction. Administration of a subclinical dose of nondepolarizing muscle relaxant has been shown to facilitate the neuromuscular effect of a subsequent dose of the same or another muscle relaxant in adults; so called the priming principle by Foldes.[1] Atracurium, a new nondepolarizing muscle relaxant of intermediate duration provides "excellent" intubation condition in children in about 2.5 min.[2], which is faster than that of pancuronium or d-tubocurarine but still slower than that of succinylcholine. The present study was undertaken to investigate the onset and duration of action of the intubation dose of atracurium preceded by a small priming dose in pediatric patients.

Method. This investigation was approved by the Institution Review Board and informed consents were obtained from parents of all the patients prior to their enrollment into the study. Thirty ASA Class I-II children under 12 years of age undergoing elective surgeries were premedicated with atropine 0.01 mg/kg I.M. and anesthetized with halothane-N_2O-O_2 by mask. After attaining a stable plane of anesthesia at 1.5% halothane, patients were randomly allocated into two groups. Group A of 15 patients received a single injection of 0.4 mg/kg atracurium I.V. and group B of 15 patients received a priming dose of 0.1 mg/kg atracurium I.V. followed by a subsequent dose of 0.3 mg/kg 6 minutes later. The degree of neuromuscular block was monitored continuously in all patients with a Datex Relaxograph EMG monitor which recorded the compound EMG response of the thumb twitch evoked by ulnar nerve stimulation with supramaximal train-of-four stimuli (2 Hz). Endotracheal intubation was performed when twitch height reached 90% depression. The intubating condition was rated by a four-point scale of excellent, good, poor or unfeasible. Anesthesia was maintained by halothane 1% in N_2O and O_2 (2:1) with controlled ventilation to keep end-tidal P_{CO_2} at 30-40 mmHg. Rectal temperature was maintained at 35-37°C. "Clinical duration" of the muscle relaxant was measured as the time from injection to spontaneous recovery of twitch EMG to 25% of control.

Results. Both groups were comparable in their demographics with age distribution of 6.55 ± 2.81 year for group A and 6.70 ± 2.45 year for group B (Table I). The onset time for 90% twitch depression was much shorter for group B, being 1.8 ± 0.5 min., than that for group A (2.9 ± 0.9 min.) and the difference is highly significant ($p < 0.001$). Conditions for intubation were rated excellent in 14/15, good in 1/15 of patients in group A, and excellent in 13/15, good in 2/15 of patients in group B. There were no significant differences between the two groups in either the maximal degree of twitch depression or spontaneous recovery time (Table II).

Discussion. Succinylcholine provides rapid onset of muscle relaxation for intubation; but being a depolarizing neuromuscular blocker, it causes many adverse cardiovascular effects, especially in children.[3] Atracurium, a nondepolarizing muscle relaxant, is shown to have minimal cardiovascular effect at the recommended clinical dose.[2] Nagashima, et al., reported that a priming dose of atracurium 0.075 mg/kg followed by 0.25 mg/kg provided good intubating conditions in 1.4 minutes in adult patients.[4] Our study demonstrated that in anesthetized children, the priming technique can also be applied to speed up the onset of neuromuscular effect of atracurium. The priming dose of 0.1 mg/kg followed by 0.3 mg/kg are within clinical range and it provides excellent intubating conditions in about 100 seconds, a significantly shorter onset time than that following single bolus dose of 0.4 mg/kg. Although still not ideal, this facilitated onset might prove beneficial in situations where a rapid sequence induction-intubation is indicated and the use of succinylcholine is deemed undesirable in pediatric patients.

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Table I

Demographic Data

Group	A (n=15)	B (n=15)
Age	6.55±2.81 yr.	6.70±2.45 yr.
Sex	9M, 6F	7M, 8F
Weight	16.4±5.2 mg	17.3±4.3 kg

II

Neuromuscular Effects (mean ± S.E.M.)

Group	A	B
Dose	0.4 mg/kg	0.1 + 0.3 mg/kg
Onset time for 90% twitch depression	2.9±0.9 min.	1.8±0.5 min.*
Maximal twitch depression	93.6±2.5%	95.2±1.9%
Clinical duration	29.7±7.4 min.	31.1±6.0 min.
Intubation condition	14/15 Excellent 1/15 Good	13/15 Excellent 2/15 Good

*$p < 0.001$

Title: A COMPARISON OF THE MATERNAL 'STRESS' RESPONSE DURING CESAREAN DELIVERY WITH GENERAL OR EPIDURAL ANESTHESIA

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Introduction. This investigation reports a comparison of the cardiovascular and hormonal changes associated with general (GA) and epidural anesthesia (EA) for Cesarean Section (CS).

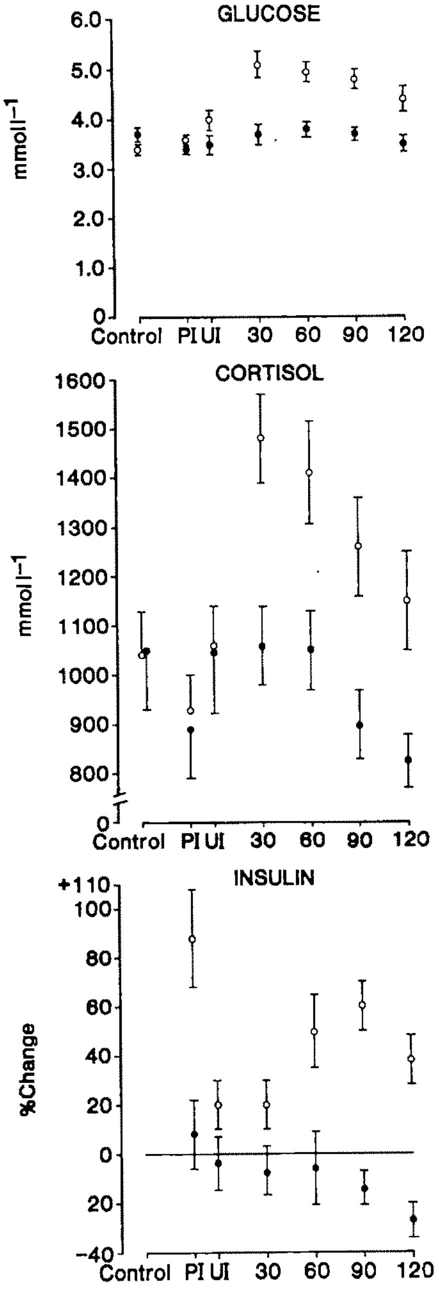
Method. This study was approved by the regional ethical committee and all patients gave informed consent. Healthy women who had an uncomplicated mature pregnancy, to be delivered by elective CS because of disproportion, received oral antacid treatment, had an i.v. infusion of 0.6 molar lactate established and were placed in lateral tilt for 30 min prior to induction of either form of anesthesia. GA consisted of pre-oxygenation, i.v. thiopental sodium dose 4-6 mg kg^{-1}, suxamethonium 75 mg and following the establishment of a cuffed endotracheal airway, nitrous oxide 50% in oxygen supplemented with 0.5% halothane. Ventilation was controlled to produce normocapnia using an endtidal CO_2 analyser and further muscle relaxation was provided by pancuronium. EA was established in the left lateral position and 0.5% plain bupivacaine was given by intermittent injection at 10 min intervals until the block reached the T_6 dermatome. These women received at least 1.0 L of the crystalloid infusion before and during the onset of the block. All patients were in left lateral tilt of 15^o to 20^o.

Maternal blood pressure and heart rate were measured before and at 10 min intervals throughout the operative period. Blood samples, drawn from the non-infusion arm, were taken before and at corresponding time intervals in the EA and GA groups for estimation of catecholamines, cortisol, glucose and insulin levels. The findings for all parameters were subjected to within and between group analysis.

Results. Twenty five women were included, 16 receiving GA and 9 EA. GA was associated with marked elevation of both systolic (+20%), diastolic (+25%), blood pressure and heart rate (+44%) immediately after endotracheal intubation. Little variation of these parameters occurred with an epidural block, except for one hypotensive episode requiring i.v. ephidrene. Marked and significant increases in adrenaline and noradrenaline levels were associated with light GA, the former being 150% and the latter 75% above their control values at the time of uterine incision. The changes in plasma cortisol, glucose and insulin are shown in Fig. 1, the elevations in those having GA being significant at various times throughout the operative period.

Discussion. This investigation shows that EA protects the parturient from the cardiovascular and hormonal changes associated with CS under GA. Regional block would seem a better method of anesthesia where cardiac or metabolic disorders complicate a pregnancy requiring CS delivery of the infant.

Figure 1. Absolute changes in plasma glucose and cortisol and % change in plasma insulin level associated with general○and epidural●anesthesia (control plasma insulin GA 5.79±0.45 ng l^{-1}; epidural 8.5±2.66 ng l^{-1}).



Title: A SURVEY OF MONITORING PRACTICES FOLLOWING SPINAL OPIATE ADMINISTRATION

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Introduction. Epidural narcotic administration requires "close monitoring" to guard against acute or delayed respiratory compromise. However, monitoring practices have not been well described in the literature. We therefore surveyed anesthesiologists about their monitoring of and experience with spinal narcotics.

Methods. A survey was sent to 110 American anesthesia departments containing questions on the use of narcotics for epidural (EN) and subarachnoid (SAN) analgesia. The following questions were asked: Do you use EN or SAN? If so, how large is your experience? In what hospital areas are EN or SAN used for acute pain problems? What patient monitoring do you use and for how long after a dose is the monitoring continued? What serious reactions have occurred? Spaces were provided for exact numbers of administrations if know. If no known, a range could be chosen. For statistical purposes, the lowest number in the range was used. Spaces were provided for comments.

Results. 73 questionaires were returned (66% response). 60 centers reported use of EN or SAN. The total experience represented was at least 6153 injections. 25% of respondents who administer regional narcotics had scant experience (less than 10). 50% had limited experience (10-100/yr.). 25% had extensive experience, performing more than 100 per year. Morphine and fentanyl are the most commonly used agents. (Table 1) Epidural narcotics were employed more commonly in pain situations than SAN. (Table 2) Most (67%) of the institutions using regional narcotics reported confining EN or SAN to the ICU setting or to specialized observation units with low patient-nurse ratios. However, 20 (33%) centers reported using En in locations classified as ward settings with limited nurse-patient contact. The locations reported for administering regional narcotics and monitoring them are listed in Table 3. Patient monitoring devices included EKG and apnea monitors (unspecified). The duration of observation ranged from 15 minutes to 48 hours (mean 18 hours).

Serious side effects reported included respiratory insufficiency (RI), respiratory arrest (RA) and death. Most complications occurred with EN. (Table 4) SAN complications were confined to reports by two centers of an unspecified number of episodes of RI without RA or death.

Discussion. Experimental studies on healthy volunteers have shown delayed and prolonged effects from spinal narcotics with blunted CO_2 responses as late as 24 hours following injection (1). However, a recent large series has reported very low incidences of respiratory complications (2).

This report suggests that some 20/110 (18%) of American departments of anesthesia are able to safely administer EN/SAN in a ward situation. Serious or fatal problems were reported to occur no less than 29/6153 administrations (.4%) overall. Among those restricting EN/SAN to intensive monitoring situations the frequency was no less than 14/2148 (.6%). Those reporting some ward use had complications at a rate of 15/4005 (.3%). Details of serious complications were not obtained. Also, the fraction of cases done in each patient care setting was not recorded. It is possible that the serious reactions occurred in relatively few ward-monitored patients.

TABLE 1: Numbers of Institutions Using Various Routes and Agents

NARCOTICS	EPIDURAL	SUBARACHNOID
Morphine	57	26
Fentanyl	32	1
Hydromorphone (Dilaudid)	7	--
Methadone	3	--
Meperidine (Demerol)	2	1
Butorphanol	2	--
Sufentanil	1	--

TABLE 2: Numbers of Institutions Reporting Uses of EN or SAN

PAIN CONDITION	EPIDURAL	SUBARACHNOID
Post-op pain management	52	13
Chronic pain	42	11
OB - post partum	26	2
OB - labor	19	4
Acute trauma	12	--
Intra-op analgesia	4	--

TABLE 3: Numbers of Institutions Reporting Various Locations for EN and SAN Use

LOCATION	EPIDURAL	SUBARACHNOID
ICU	47	9
PAR	38	4
Supervised OB Unit	24	--
Ward	20	--
Operating Room - only	17	1

TABLE 4: Serious Complications (EN Only)

MONITORING OR USE (Reported Administrations)	COMPLICATION		
	RI	RA	DEATH
ICU only (2148)	>12	1	1
Ward and ICU (4005)	>10	4	1
All (6153)	>22	5	2

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Title: PREOXYGENATION IN THE MORBIDLY OBESE PATIENT

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Introduction. Preoxygenation with 100% O_2 for 3 to 5 minutes with subsequent denitrogenation of the lungs has become a common practice prior to induction of a general anesthetic. Gold et al in 1981 demonstrated in healthy volunteers that 5 minutes of 100% O_2 or 4 deep breaths of 100% O_2 raised arterial oxygen tension (PaO_2) above 340 mm Hg.[1] More recently two groups have extended this to the parturient at term.[2,3] Both groups concluded that for the parturient, either technique was equally effective in increasing PaO_2 prior to induction of general anesthesia. The purpose of this study was to examine the effectiveness of preoxygenation techniques in a population with a characteristic pattern of pulmonary derangement, the morbidly obese patient. Pulmonary derangements in the morbidly obese include decreased compliance, increased work of breathing, reduced respiratory muscle efficiency, altered distribution of ventilation, decreased lung volumes (particularly FRC), and increased oxygen consumption. In addition to pulmonary changes these patients are at increased risk of acid aspiration. Under such circumstances a rapid sequence induction with Sellick's maneuver is recommended. Such a technique relies on preoxygenation to provide protection against hypoxemia.

Methods. Approval was obtained from the Committee on the Conduct of Human Research. Informed consent was obtained from 13 morbidly obese patients free from additional cardiopulmonary disease, scheduled for elective abdominal surgery under general anesthesia. Narcotics were excluded from all preoperative and induction medications. A 20 gauge radial arterial line placed prior to induction was used for all blood sampling. 100% O_2 was delivered via a circle system at 8 l/min. flow. The OR table was placed in a 15-degree reverse Trendelenberg position. Patients were randomly assigned to one of two groups. Group I (n=7), arterial blood gases (ABG) were drawn following each measurement condition in this sequence: 1) room air (baseline), 2) 3 minutes tidal breathing 100% O_2, 3) 5 minutes of room air (return to baseline), 4) 4 maximal deep breaths of 100% O_2 over 30 seconds, 5) after endotracheal tube placement and prior to ventilation. The sequence of conditions 2 and 4 were reversed in Group II (n=6). Results were analyzed utilizing an analysis of variance and Bonferroni t-statistics.

Results. A significance level of p 0.05 was considered statiscally significant. There was no significant difference between Group I and II with respect to PaO_2 after 4 maximal deep breaths of 100% O_2 or after 3 minutes of tidal breathing of 100% O_2, therefore the results for both groups were pooled. Table I shows the mean PaO_2 for each experimental condition (pooled data). There was no significant difference between the mean PaO_2 of either preoxygenation method. There was no significant difference between the baseline PaO_2 and the return to baseline PaO_2 (maneuver 3). The mean PaO_2 after intubation was significantly different from both the baseline and preoxygenation maneuvers.

Discussion. The results of our study indicate that both methods are effective in raising the PaO_2 of the morbidly obese patient to levels consistently above 300 mm Hg. The range of PaO_2 on intubation revealed wide variation and served to underscore the importance of the margin of safety afforded by preoxygenation of the morbidly obese. The results of our study demonstrate that this method (4 deep breaths) of preoxygenation is effective in a patient population with a characteristic pulmonary derangement. We feel that the advantages of being able to adequately preoxygenate over a relatively short period of time are beneficial, particularly in the anxious or emergency patient.

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Table I: Mean PaO_2 with various preoxygenation techniques (pooled data)

	Mean PaO_2 (mm Hg)	Code*
4 deep breaths	437.5	A
100% O_2 x 3 min	413.3	A
room air x 5 min	96.9	B
baseline	92.5	B
post intubation	235.8	C

* means with the same letter code are not significantly different

Table II: Comparison of groups mean PaO_2 with various preoxygenation techniques

	Group I (n=7)	Group II (n=6)
baseline	90.6 ± 5.5	94.8 ± 5.3
100% O_2 x 3 min	368.3 ± 55.2	459.2 ± 45.6
room air x 5 min	94.6 ± 6.0	99.7 ± 7.0
4 deep breaths	418.8 ± 32.2	465.8 ± 20.3
post intubation	236.4 ± 68.4	235.2 ± 56.6

TITLE: **CEREBRAL BLOOD FLOW, OXYGEN CONSUMPTION AND EEG DURING ISOFLURANE ANESTHESIA**

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INTRODUCTION

Isoflurane is unique amongst currently available inhalational anesthetics in that in clinically relevant concentrations it can induce an isoelectric EEG without the production of seizure activity. We investigated the effects of this agent on cerebral blood flow (CBF), oxygen consumption (CMRO$_2$) and the EEG to determine whether it can improve cerebral oxygen supply-demand balance.

Methods

Following institutional approval and after obtaining written informed consent, 7 patients (mean age 30±9 years) undergoing closed-heart surgery for ablation of accessory conducting pathways (Wolff-Parkinson-White syndrome) were studied. Patients were premedicated with either morphine 0.15 mg/kg I.M. and lorazepam 0.06 mg/kg P.O. or demerol 1 mg/kg I.M. 90 minutes prior to surgery. In addition to radial artery and central venous pressure catheters, a catheter was inserted percutaneously via the right internal jugular vein into the jugular foramen for sampling effluent cerebral venous blood. Cerebral blood flow was determined using an inert gas washout technique utilizing ^{133}Xe and an array of 10 scintillation detectors, 5 over each cerebral hemisphere. CBF values were corrected for changes in temperature and hematocrit. CMRO$_2$ was calculated from the arterial-jugular O$_2$ content difference and the mean right hemispheric CBF. The EEG was continuously recorded on a Nihon-Kohden polygraph utilizing a 10-channel bipolar parasagittal montage with sensitivity of 7μV and a paper speed of 15-30 mm/sec. Control measurments were made prior to induction of anaesthesia with the patients breathing 100% of O$_2$. After induction of anaesthesia with thiopental 5 mg/kg and pancuronium 0.10 mg/kg, the patients were intubated and ventilated with 100% O$_2$ and isoflurane. Following a minimum of 30 minutes ventilation with 2.5% inspired isoflurane, repeat hemodynamic and CBF measurements were obtained. Data were analyzed by an unpaired t-test where $p<0.05$ is significant.

Results

(see table) All patients tolerated anaesthesia and surgery without problem. In 2 patients control CBF measurements were not obtained as a tight mask fit was not achieved producing an uninterpretable ^{133}Xe air-curve. Control EEG showed a normal background of low-voltage alpha activity while 2.5% inspired isoflurane induced burst-suppression in 5 of the patients with periods of uninterrupted isoelectric activity lasting up to 12 minutes in 2 patients. Two other patients displayed irregular high-voltage activity of 100-150 μV amplitude and 3-6 c.p.s. frequency throughout the study and did not exhibit burst-suppression even following prolonged inhalation of 3.5% isoflurane. Overall 2.5% isoflurane did not significantly lower CBF while CMRO$_2$ was reduced by nearly 50%.

Conclusions

In most patients inhalation of 2.5% isoflurane produces a characteristic burst-suppression EEG pattern and is capable of inducing a significant reduction in CMRO$_2$ while maintaining CBF at pre-anaesthetic values. These results confirm in man what has previously been demonstrated in animals.[1]

Reference

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TABLE (mean±S.D.)

	CONTROL	2.5% ISOFLURANE
n (Patients)	5	7
CBF (ml/100g/min)	46.3±4.9	44.5±6.8
CMRO$_2$ (ml/100g/min)	2.47±0.39	1.29±0.26$^{\phi}$
CPP* (mm Hg)	89±10	69±15^{+}
CO$_2$ (mm Hg)	39±5	38±6
TEMP (°C)	36.6±0.4	35.8±0.5^{+}

(*CPP = mean arterial pressure minus jugular pressure)
$^{+}p<0.05$; $^{\phi}p<0.001$

Supported in part by grant no. 84-41 from P.S.I. Foundation and a grant from U.W.O. Second Century Fund.

Title: POST-ANESTHETIC SHIVERING: INCIDENCE, AND IMPLICATIONS IN THE ELDERLY PATIENT

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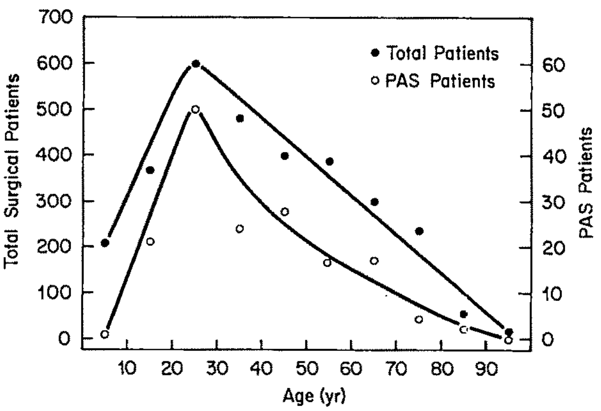
Introduction. Post-anesthetic shivering (PAS) a well-known clinical phenomenon, can cause many post surgical complications, including hypoxemia and infarct (1-4). Patients particularly at risk include those with pre-existing compromised cardiovascular and/or pulmonary systems. Since the incidence of many heart, lung and vascular diseases increases with age, the present study was designed to determine the incidence of PAS relative to age.

Methods. After approval of the study by the local Human Research Internal Review Board, patients admitted for elective surgery were observed post-operatively for significant shivering. Data were then collected over a five month period and the proportion of the patients experiencing PAS was tabulated by age. Recovery room personnel recording PAS occurrence as well as operating room personnel were blind to the purpose of the study. Linear correlation techniques were used to evaluate the data.

Results. Anesthesia used in the 3,060 cases surveyed included narcotic, volatile and mixed narcotic/volatile (balanced) techniques. Surgeries included orthopedic, abdominal, gynecologic, peripheral, vascular, neural and ENT procedures. PAS was observed in 165 cases, in patients under 10 yr to greater than 80 yr of age. Whereas the peak incidence of PAS occurred in 20-30 yr group, the ratio of PAS incidence to total cases remained relatively constant from the second through the eighth decades (r = 0.91). Average (± S.D.) incidence of PAS was 5.3 ± 2.0% of all surgical cases; [range 8.3 (second decade) to 1.8% (seventh decade)].

Discussion. The results indicate that the incidence of PAS in surgery patients remains relatively constant throughout the life span. With rapidly increasing developments in medical technology and surgical capabilities, more elderly patients are undergoing elective surgical procedures which would not have been considered previously. Considering the often compromised physical condition of the aged, the increased demand on cardiovascular and pulmonary systems caused by PAS in the elderly can be life-threatening. Therefore, particularly in the elderly patient, care must be taken both during and after surgical procedures to prevent or minimize the deleterious effects of PAS.

PAS VS. AGE



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(Research supported by the Biological Humanics Foundation.)

Title: ASSESSMENT OF STERILITY OF PULMONARY ARTERIAL CATHETER SHEATHS

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Introduction: The pulmonary arterial catheter (PAC) has become a cornerstone for hemodynamic monitoring in the ICU. As the PAC is more frequently used, a subset of patients arises in which, after an initial monitoring success, the catheter fails to wedge. The best way to reposition the catheter in this circumstance is the subject of debate (1).

Kopman and Sandza developed a plastic sleeve that was put over the catheter at the time of introduction (2). The sleeve was reported in 10 patients to preserve the sterility of the catheter that remained outside the patient but within the sheath.

However, the authors failed to report whether any of the catheters were manipulated within the sheath prior to the cultures being obtained. Furthermore, swabbing the PAC, as they did, may not be the most effective way to assess the sterility of the catheter. Finally, the number of catheters studied may have been too small to adequately detect contamination.

The purpose of this study then was to assess, by two different techniques, whether the currently marketed contamination sheaths do indeed safeguard the sterility of the portion of the PAC that lies outside the patient.

Methods: After approval by the Institutional Review Board 42 patients were studied. Only patients undergoing major vascular surgery were included. Patients in whom the PAC was manipulated within the sheath after insertion and before termination of invasive monitoring, were excluded.

Following skin preparation with povidone-iodine and draping with sterile towels, the PAC, with the contamination sheath attached, was placed through an introducer in the internal jugular or subclavian vein. Procedures were performed prior to surgery by physicians wearing caps, masks, sterile gloves and gowns.

The duration of pulmonary arterial catheterization and the results of blood or catheter tip cultures were recorded for each patient. At the time that hemodynamic monitoring was discontinued, the proximal contamination sheath was swabbed with isopropyl alcohol and 10 ml of nonbactericidal D5LR were injected into the sheath, agitated and withdrawn.

The sheath was then cut in two to expose 5 cm of the PAC immediately outside the introducer. Using sterile scissors this portion of catheter was severed and placed in a sterile test tube. In the laboratory it was rolled across a chocolate blood agar plate (CBAP) utilizing Maki's semi-quantitative technique (3). The catheter was then dropped into a test tube containing enriched brain heart infusion broth (EBHIB). The fluid was inoculated on CBAP with a 0.01 ml loop for quantitative assessment. An additional 0.1 ml aliquot was inoculated in EBHIB. All media were incubated at 35°C in 5-10% CO_2 for seven days. Cultures were examined daily. The catheter segment or fluid was culture positive if either the EBHIB or the CBAP had evidence of bacterial or fungal growth. When the CBAP's were positive, the number of colony forming units (CFU) were reported.

Results: Of the 42 patients studied seven patients (17%) had catheter segments that were positive for bacterial growth. Of these 7 only one was positive in EBHIB. Of the 6 positive by the semi-quantitative technique, 3 had less than and 3 greater than 15 cfu/ml.

An additional 5 of 42 patients (12%) had the fluid wash of the sheath positive for bacterial growth. All 5 were positive in EBHIB only.

In no patients were both the sheath fluid and the catheter segment positive. None of the total of 12 patients (29%) with positive cultures, had a positive culture of the tip of the PAC (routinely performed at our institution). None had evidence of septicemia nor were any cultures (blood, wound, urine) from patients positive for the same organism growing on the PAC segment or within the contamination sheath. There was no correlation between duration of catheterization and the likelihood of a positive culture.

Discussion: Others have found a 14% incidence of positive sleeve cultures, culturing only the segment of catheter contained within the sleeve, which correlates with our 17% incidence of infection for the catheter itself (4). In addition we found another 12% of patients who had evidence of bacterial growth within the contamination sheath. While we found no evidence of clinical sequelae, our results draw into question whether these catheters can be safely manipulated within the sheaths after placement. There was no evidence that sterility was maintained up to a certain point in time, as the frequency of positive cultures was the same before 24 hours as afterwards.

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Title: EFFECT OF PREMEDICATION ON ARTERIAL BLOOD GASES IN CARDIAC SURGICAL PATIENTS

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Introduction. Arterial hypoxemia following preoperative sedation may increase the risk of myocardial ischemia in patients undergoing aortocoronary bypass procedures. Previous studies on preoperative oxygenation have shown conflicting results following a premedication using a narcotic with scopolamine (1,2). The effect of such premedication in combination with lorazepam as frequently used in our center have not been reported. We undertook a double blind clinical trial to assess the effect of morphine and scopolamine with or without lorazepam on preoperative arterial blood gases.

Methods. The study protocol was approved by the Human Research Ethics Committee of our institution and informed written consent was obtained. Forty patients (range 40 to 67 years of age) scheduled for elective coronary artery bypass were randomly divided into two groups. Patients included had stable angina without heart failure or significant pulmonary disease. Three patients were excluded because of delayed or cancelled surgery. Two hours before surgery group I (n=19) received oral placebo and group II (n=18) received oral lorazepam 2 mg (40-59 kg), 3 mg (60-79 kg) or 4 mg (>80 kg). One hour before surgery both groups received intramuscular scopolamine 0.4 mg and morphine 7.5 mg (40-59 kg) or 10 mg (>60 kg). Two arterial blood gases were obtained with the patient in the supine position breathing room air. The first was taken prior to the day of surgery and the second taken one hour after morphine and scopolamine injection. The PaO_2, $PaCO_2$ and pH were recorded. Statistical analysis was done with the student's t-test to compare blood gas results within each group and between the groups. A $p<0.05$ was considered statistically significant.

Results. The patients were matched in each group for age, sex, weight and height. Within the placebo group the PaO_2 fell 6.6 ± 2.1 mm Hg after the premedication from a baseline value of 80.2 ± 1.9 mm Hg ($p<0.005$). In the same group the $PaCO_2$ rose 2.7 ± 0.8 mm Hg ($p<0.005$) and the pH was not significantly changed. In the lorazepam group the PaO_2 fell 6.9 ± 2.2 mm Hg after the premedication from an initial value of 77.1 ± 1.4 mm Hg ($p<0.01$). The $PaCO_2$ rose 2.5 ± 0.6 mm Hg ($p<0.001$) and the pH fell 0.012 ± 0.005 ($p<0.05$). However between the two groups, there were no significant differences in average PaO_2, $PaCO_2$, and pH as measured before the day of surgery and following the premedication.

Discussion. Premedication with morphine-scopolamine in otherwise healthy cardiac surgical patients results in a reduction of PaO_2 and a rise in $PaCO_2$. The addition of lorazepam to allay anxiety and induce amnesia does not potentiate these changes in arterial blood gases. Even though the average changes are statistically significant, they are not clinically important. The decrease in PaO_2 occurs on the flat part of the oxyhemoglobin dissociation curve thus producing little change in saturation. As previously noted the decrease in PaO_2 following a narcotic premedication cannot be explained on the basis of a rise in $PaCO_2$ alone (3). This discrepancy has been related to an alteration in lung mechanics (4).

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Table. Arterial blood gases (Mean ± SEM)

		Group I (n=19) placebo	Group II (n=18) lorazepam	
PaO_2*	pre	80.2 ± 1.9	77.1 ± 1.4	NS
	post	73.6 ± 2.1	70.2 ± 2.6	NS
		$p<0.005$**	$p<0.01$**	
$PaCO_2$*	pre	38.9 ± 0.7	39.9 ± 0.5	NS
	post	41.6 ± 0.8	42.4 ± 0.7	NS
		$p<0.005$**	$p<0.001$**	
pH	pre	7.424 ± .004	7.430 ± .006	NS
	post	7.413 ± .004	7.418 ± .004	NS
		NS	$p<0.05$**	

pre = before premedication; post = after premedication; NS = not significantly different
* mm Hg
** significant difference between pre and post values

Title: SODIUM THIOPENTAL KINETICS DURING CARDIO-PULMONARY BYPASS.

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Introduction. Cardiopulmonary bypass exerts profound physiologic effects because of hemodilution, hypothermia and non-pulsatile perfusion, which have potential in altering the response and disposition of drugs that are routinely used in these patients (1). Pharmacokinetics of Thiopental (TP) in normal volunteers and those undergoing minor surgical procedures is well documented (2&3), but no kinetic information is available during CPB. However, there is widespread concern regarding its use in patients undergoing CPB because of the fear of myocardial depression and adverse hemodynamic effects. We have investigated the alterations in the pharmacokinetics of TP in twenty patients undergoing CPB to assess the usefulness of this drug in open heart surgery patients.

Methods. Following an approved protocol from the clinical research committee on human research, we selected twenty adult patients, (mean age 53 years, 12 male and 8 female) undergoing surgery for coronary artery bypass graft or cardiac valve replacement. Anesthetic techniques consisted of high dose fentanyl or Morphine-Valium with Pavulon and 100% oxygen ventilation, after establishing appropriate monitoring. After cannulation, the patients were connected to CPB machine and total body hypothermia of 25-26°C was acheived. The aorta was cross clamped and cardiac arrest induced with cardioplegic solution. At this stage, TP (6 mgs/kg) was administered IV as a bolus, and blood samples were collected upto 90 minutes (Table 1).

Plasma levels of TP were measured using a specific HPLC procedure that employs UV detection, (280 n m) and carbamazapine as internal standard. The kinetic analysis was performed by simulating the previously proposed TP model of Burch & Stanski (4) and fitting their model to our mean data using SAAM (simulation analysis and molding) program that employs iterative non-linear least squares regression for parameter estimation. Total body clearance (CLt) and metabolic clearance (CLm) were computed using standard equations and area analysis techniques. The fraction of TP metabolized was computed from the ratio of CLm to CLt.

Results. Following the administration of TP to patients under CPB the mean plasma level at 1 min was 21.9 (±sem 2.2) micrograms/ml and declined 4 to 6 fold during the procedure. Table 1 shows the mean TP levels as a function of our sampling schedule in all 20 patients with the associated 20-40% variability. Under the assumption that the disposition rate (lamda Z) associated with TP elimination has been previously established [lamda Z = 0.06/hr; t 1/2 = 11.5 hrs (3&4)] the present kinetic evaluation was performed.

The initial distribution volume of the Central pool (Vc) and the hybrid distribution rate constants (lamda 1 and lamda 2) for TP had means of 16 liters, 0.22 and 0.011/min, respectively. The CLt in these patients had a mean of 0.080 (±sem 0.005) liters/min while the CLm during CPB contributed 5 to 16% of the total loss (Table 1). Both CLt and CLm indicate diminished metabolism during CPB.

Discussion. As is evident from Table I, mean plasma TP concentrations achieved during this study are comparable to previously published disposition profiles. Mean Vc estimated for TP in central compartment of 16 liters compares favorably with 13.2 liters reported by Morgan et al (3). Estimates of drug distribution rates (lamda 1 and lamda 2) are also in close agreement with previous reports (3&4). The total clearance (CLt) of TP in our patients (0.08 liters per minute) appears to be significantly (P<0.001) reduced and is about 50% lower when compared to normal volunteers (0.164 liters per minute) (2) and those undergoing minor surgery (0.150 liter per minute) (3&4). Although proportional decrements are observed in CLm, drug distribution phases probably associated with the anesthetic effect appear to be unchanged. Therefore, the myocardium is exposed to low TP levels and shows no myocardial depressant or adverse hemodynamic effect.

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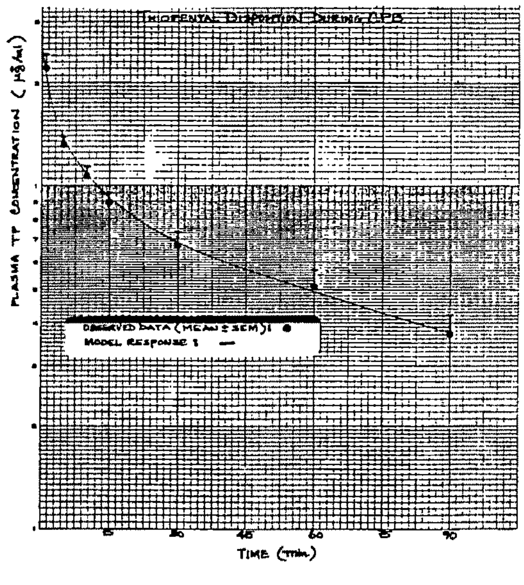
TABLE I

PLASMA THIOPENTAL LEVELS AND KINETICS DURING CPB

	Time(min)						
Parameter	1	5	10	15	30	60	90
MEAN (ug/ml)	21.9	13.1	10.7	8.9	6.7	5.1	3.7
SEM	2.2	0.9	0.7	0.6	0.6	0.6	0.5
% CV	45	31	28	30	40	40	27
ML (mg)	2.1	8.4	13.8	18.2	28.7	44.7	56.6
fm	0.05	0.05	0.06	0.07	0.10	0.14	0.16

fm = Metabolic loss (ML)/total loss



Title: SYSTEMIC RESISTANCE AND REWARMING TIME FOLLOWING HYPOTHERMIA FOR OPEN HEART SURGERY IN INFANTS: NITROPRUSSIDE AND/OR DROPERIDOL

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Introduction. Rewarming following hypothermic cardiopulmonary bypass (CPB) and rapid re-establishment of cardiac function with normothermia is an important contributing factor in reducing morbidity and mortality following surgical repair of congenital cardiac malformations in infants. Currently a variety of techniques and pharmacologic agents are used to facilitate rapid restoration of normothermia during the rewarming process. Both sodium nitroprusside (SNP) and/or droperidol (D) have been used for this purpose. However, no controlled studies are available comparing these two techniques with regard to the duration of rewarming time and effects on the systemic vascular resistance. Consequently, we studied the effects of SNP alone and a combination of SNP AND droperidol on the duration of rewarming time and systemic vascular resistance following hypothermic CPB in infant undergoing open heart surgery.

Methods. After approval of the Human Investigation Committee, fifteen infants (n = 15) with congenital cardiac anomalies undergoing open heart surgery with profound (20°C) or mild (20°C-30°C) hypothermia during CPB were studied. These 15 patients were randomly assigned to SNP (Group 1, n = 8) or SNP/D (Group II, n = 7). General anesthesia was induced and maintained with endotracheal intubation in the same manner for all patients in both groups. Anesthetics consisted of N_2O/O_2/pancuronium and halothane or morphine. During CPB hypothermia was induced by the core cooling method. After surgical correction and the onset of rewarming, SNP (1-5 ug/kg/min) was infused to the patients assigned to Group 1 and SNP (1-5 ug/kg/min) plus droperidol (100 ug/kg, bolus, i.v.) to Group II. Data regarding rewarming time, perfusion pressure and flow, as well as regional temperatures (esophageal, rectal and tympanic) were obtained every three minutes until the rectal temperature reached 35°C at which time CPB was terminated. The systemic vascular resistance index (SVRI, mmHg/l/min/m^2) was calculated on the basis of mean arterial pressure and CPB pump flow. Data were collected and compared using paired t test ($P < 0.05$ was considered significant).

Results. The two groups were comparable for age, weight, and body surface area. The degree of esophageal, rectal and tympanic temperature changes during the core rewarming process was not significantly different ($P > 0.05$) between Group I and Group II, i.e., 17.3 vs 18.7°C (esophageal), 12.9 vs 13.7°C (rectal), and 15.3 vs 17.2°C (tympanic). However the rewarming time was significantly prolonged in Group I as compared with Group II (52.5 ± 5.69 vs 35.9 ± 3.02 min, $P < 0.05$, Fig. 1). Thus, the time required to increase per degree (°C) of rectal temperature in Group I and Group II was 4.07 and 2.62 min/°C, respectively ($P < 0.05$). The SVRI decreased significantly ($P < 0.02$) after rewarming in both groups (12.9 ± 1.01 vs 19.0 ± 5.64 or 36 vs 44%, Fig. 2); however, between groups the differences were not statistically significant ($P > 0.05$). No serious adverse effects occurred in association with administration of these two agents.

Discussion. Administration of vasodilators such as SNP and/or droperidol during rewarming process following hypothermia is well established and widely accepted. SNP used alone in the range of 1-5 ug/kg/min has not been uniformly satisfactory in decreasing the duration of rewarming time. While a prolonged rewarming itself may not always result in serious postoperative complications, it may exacerbate the restoration of cardiovascular function after prolonged hypothermia. Higher doses of SNP, close to the toxic dose range, may be required if SNP is used as a sole agent. The data obtained in this study suggest that the routine use of droperidol in combination of SNP is beneficial for shortening the rewarming time.

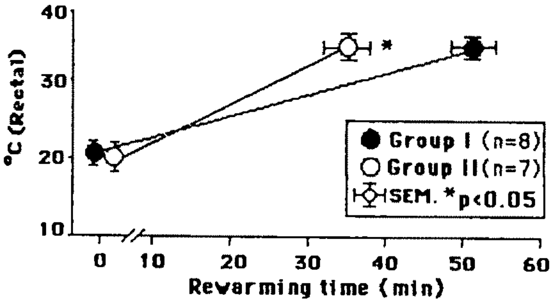

Fig.1 Duration of rewarming vs temperature

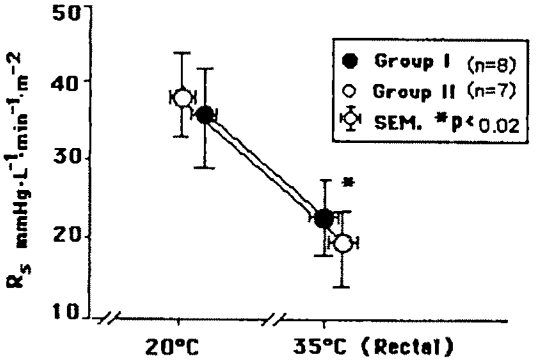

Fig.2 Changes of Rs (systemic resistance) before and after rewarming.

Title: DOES SERUM K+ LEVEL CHANGE AFTER CARDIOPLEGIA DURING CARDIOPULMONARY BYPASS IN PEDIATRIC OPEN HEART SURGERY

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Introduction. The role of cardioplegic solution (CP) in myocardial protection during cardiopulmonary bypass (CPB) has been well recognized. A major limitation related to the use of CP is prolongation of hyperkalemic effects on cardiac impulse formation, conduction and contraction. In contrast, the disturbing dysrhythmic effects of hypokalemia were speculated in adults. Whether the same can be applied to pediatric patients has not been investigated. This study was designed to measure the change of serum potassium concentration following administration of CP during CPB in pediatric open heart surgery.

Methods. Twenty seven patients (n=27) who underwent open heart surgery for correction of congenital anomalies were reviewed retrospectively with approval of the Human Investigation Committee. After an appropriate premedication for all patients endotracheal general anesthesia was induced and maintained using nitrous oxide, oxygen, pancuronium and morphine or halothane. All patient's ventilation were controlled and their acid base balance were monitored continuously. A sample of arterial blood was obtained via an established indwelling arterial line to measure serum potassium and hematocrit levels prior to surgical incision and they were used as the baseline control. Five and 30 min following administration of cold CP and after the completion of CPB when the patient was hemodynamically stable blood samples were obtained. The total duration of CPB and aortic cross clamp time, amount of CP used, and lowest esophageal temperature during CPB were also recorded. The CP consisted of K+ 25 mEq/L, chloride 25 mEq/L, dextrose 5.6 g/L, and mannitol 12.5 g/L. The prime for CPB consisted of lactated Ringer's solution, mannitol, whole blood, fresh frozen plasma, calcium chloride, kefzol and heparin. Age, body weight, body surface area, the total duration of CPB and the aorta cross-clamp time, the cooling esophageal temperature, the amount of CP and prime used are listed in Table 1.

Results. The control mean serum K+ concentration of 3.9 mEq/L increased to 4.6 and 4.2 at 5 and 30 min respectively following CP; however, only the increase at 5 min following CP was statistically significant (Student t test, $p < 0.05$, Table 2). Significantly lower level of hematocrit was maintained throughout CPB as compared with the control ($p < 0.01$, Table 2). Patients did not require supplementary K+ administration for hypokalemia or treatment for hyperkalemia during surgery. Twenty six of the twenty seven (26/27) patients maintained K+ level in a physiologically acceptable range. However, one patient, in which serum K+ level (control of 3.5 mEq/L) increased to 7.2 mEq/L at 5 min following CP, developed a supraventricular tachycardia but it was controlled by direct internal cardioversion. His serum K+ remained at a level of 5.5 mEq/L after CPB.

Discussion. Cardioplegia plus induced hypothermia has been routinely used during CPB to prevent myocardium from high energy phosphate utilization. Since potassium-rich cardioplegia is used during CPB it is speculated that some of K+ may enter the circulation when systemic perfusion resumes with resulting hyperkalemia. In contrast, the uptake of potassium by cells during CPB and induced hypothermia may lead hypokalemia. In this study neither hyperkalemia nor hypokalemia was observed despite the presence of induced hemodilution. This study suggests that clinically insignificant amounts of potassium despite a large amount used in cardioplegia may enter the systemic circulation when perfusion resumes. Supplementary potassium may rarely be required in the immediate postoperative period in infants and children.

Table 1
Age, weight, surface area, CPB and aortic cross-clamp time, lowest esophageal temp, and amount of CP and prime used. (n = 27)

	Mean + SEM	Range
Age (month)	28.9 ± 7.0	2 days-10 yrs
Weight (kg)	12.1 ± 1.83	2.8-48.0
BSA (m^2)	0.58 ± 0.04	0.13-1.36
CPB (min)	86.4 ± 6.26	27-151
Aortic Clamp (min)	44.9 ± 3.19	15-80
Temp (E,°C)	21.5 ± 1.02	15-32
CP used (ml)	210 ± 29.3	50-650
Prime used (ml)	1288 ± 49.6	950-2095

Table 2
Serum K+ and hematocrit levels
(n = 27, mean ± SEM, **$p < 0.05$, *$p < 0.01$)

	K+ (mEq/L)	Hct (%)
Control	3.9 ± 0.09	37.6 ± 1.14
5 min CP	4.6 ± 0.15**	29.1 ± 0.79*
30 min CP	4.2 ± 0.49	26.2 ± 0.77*
10 min off CPB	4.1 ± 0.12	26.9 ± 0.54*

Title: THE INFLUENCE OF THE RESPIRATORY RATE ON THE RATIO OF PHYSIOLOGICAL DEAD SPACE TO TIDAL VOLUME

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Introduction. The ratio of the physiological dead space to the tidal volume (VD/VT) remains relatively constant in normal man (1). For this reason, VD/VT has been used as one of the important criteria for weaning from the mechanical ventilator therapy. However, there have been some controversial studies (2,3), reporting that the VD/VT did change when the inspiratory time of the ventilator was altered. In the present study, we examined the effects of different respiratory rates on the VD/VT in patients with respiratory failure who have been subjected to prolonged respiratory therapy.

Methods. Seven consenting, lightly sedated patients were studied with institutional approval. All patients were intubated and placed on the mechanical ventilator (Siemens-Elema Servo 900C). In each patient, the dial settings of the ventilator were made as following: inspiratory time: 25%, inspiratory pause time: 10%, and expiratory time: 65% for each respiratory cycle respectively. End-tidal CO_2 fraction and total CO_2 production were measured with a Siemens-Elema 930 CO_2 analyzer. Expiratory volume was measured with a hot wire flowmeter (Minato Medical Science RM-200) via a tracheal tube. The ratio of the VD/VT was calculated using Enghoff's modification of Bohr's equation: $(PaCO_2-PECO_2)/PaCO_2$, where $PaCO_2$ denotes arterial PCO_2, and $PECO_2$ is the mixed expired PCO_2. After stabilizing over 20 minutes, measurements were made at 4 different respiratory rates of 10, 20, 30, and 40 breaths/min. In order to maintain constant $PaCO_2$, each tidal volume was adjusted accordingly. The data were analyzed using the paired t-test accepting $p< 0.05$ as significant.

Results. As shown in the figure, when the respiratory rate was increased, the VD/VT augmented significantly because the physiological dead space (VD) remained unchanged despite the significantly decreased VT.

Discussion. In normal subjects, changes in VT are accompanied by a concomitant change in VD, so that VD/VT ratio remains unchanged when the respiratory parameters are altered. However, if VT decreases extremely, VD/VT augments because of the fixed VD which already reached the low limit. If VT was large enough, the VD/VT ratio would have remained unchanged. In our ill, mechanically ventilated patients, the large VD which was already decreased to the minimal values was not affected by even the significant decrease of VT values. Therefore, the VD/VT ratio elevated progressively and significantly with increased respiratory rate. The smallest VT used in our patients was 5.7 ± 1.01 ml/kg at 40 breaths per minute. Thus, it is suggested that, in addition to the VD/VT ratio, other respiratory parameters should be also seriously considered, particularly when assessing the respiratory function for weaning from mechanical ventilatory support in patients with respiratory failure.

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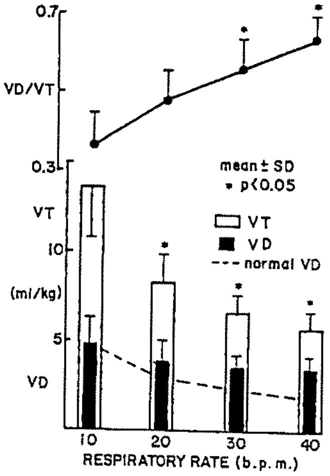

Title: PHENOBARBITAL PREVENTS LOSS OF CEREBRAL BLOOD FLOW AUTOREGULATION AFTER ASPHYXIA IN NEWBORN LAMBS

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Introduction. Autoregulation of cerebral circulation normally maintains cerebral blood flow (CBF) constant despite changes in systemic blood pressure. In preterm neonates, loss of autoregulation allows CBF to vary with fluctuations in arterial blood pressure and may lead to intracranial hemorrhage (IVH), death or central nervous system damage[1]. Phenobarbital has been reported to be effective in prevention of IVH in premature infants[2]. However, others have failed to confirm such beneficial effects. Therefore, we assessed the effects of phenobarbital on CBF and its autoregulation after a period of asphyxia in newborn lambs.

Methods. Eleven 1-3 day old lambs were anesthetized with 70% N_2O, 30% O_2 and paralyzed with d-tubocurarine. The skin of their groin and neck was anesthetized with 1% lidocaine for insertion of catheters into the femoral artery, and vein as well as lingual artery. Xenon was injected through the lingual artery and xenon washout from the brain was measured with a gamma counter placed over the right parietal area. CBF was derived from the initial slope of the xenon washout curve. CBF autoregulation was assessed by determining CBF at normal, elevated and decreased mean arterial blood pressures (MAP) before asphyxia (BA) and after asphyxia (AA). MAP was increased by infusion of 0.02% phenylephrine solution and decreased by infusion of 0.1% sodium nitroprusside. After surgical preparation, the lambs were allowed to recover for 2 hours. After stabilization and demonstration of normal CBF autoregulation, the lambs were subjected to 30 minutes of asphyxia (PaO_2 25-30 mmHg, $PaCO_2$ 60-70 mmHg). At 20 minutes after the start of asphyxia, 6 lambs received phenobarbital 20 mg/kg i.v. over 5 minutes. After asphyxia, all lambs were maintained at normoxia and normocapnia for the duration of studies. Data were compared by analysis of variance.

Results. The CBF data are presented in the table. During asphyxia, CBF increased significantly. In the untreated lambs, at 30, 90 and 150 minutes after the end of asphyxia, CBF increased with MAP elevation and at 30 minutes after asphyxia, CBF decreased with MAP reduction. These changes indicate impairment of autoregulation in the untreated lambs. The phenobarbital treated lambs maintained fairly constant CBF at all times after asphyxia despite increases and decreases in systemic blood pressure, indicating normal autoregulation. CBF at resting MAP decreased after asphyxia in both groups, but the decrease in CBF of untreated lambs occurred later, being significant only at 150 minutes after asphyxia.

Discussion. These results confirm our previous studies which showed impairment of CBF autoregulation after asphyxial stress in newborn lambs. The response to decrease in MAP was not assessed previously. The present study indicates that CBF did not decrease with MAP reduction after 30 minutes post-asphyxia while CBF continued to increase with MAP elevations. The different responses may be caused by a shift in the CBF-MAP autoregulation curve to the left or may represent the activation of a secondary mechanism to maintain CBF above a critical level. Further studies on this aspect are required. The phenobarbital treated lambs maintained normal autoregulation after asphyxia but had a decreased level of cerebral perfusion. The hypoperfusion is probably caused by the depressant effects of phenobarbital on cerebral metabolism. The cause of the delayed cerebral hypoperfusion in the untreated lambs may represent a delayed response to asphyxia. Our results indicate that phenobarbital has a protective effect for CBF autoregulation in asphyxiated newborn lambs which may explain the reported reduction in IVH after phenobarbital treatments in human neonates.

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CBF (ml/100g/min, mean ± S.E.M.)

	Untreated Lambs	Phenobarbital treated lambs
Before asphyxia		
Decreased MAP	59.4 ± 4.6	73.8 ± 6.5
Normal MAP	63.8 ± 5.4	74.3 ± 6.7
Elevated MAP	64.4 ± 5.1	73.8 ± 7.2
During aphyxia		
Normal MAP	219 ± 12.5**	210.6 ± 8.1**
30 min. after asphyxia		
Decreased MAP	54.0 ± 4.6#	45.0 ± 2.1
Normal MAP	64.0 ± 7.1	48.8 ± 3.1**
Elevated MAP	77.2 ± 9.1##	50.2 ± 3.2
90 min. after asphyxia		
Decreased MAP	49.8 ± 1.9	47.7 ± 1.8
Normal MAP	56.8 ± 4.0	49.0 ± 1.9**
Elevated MAP	66.8 ± 8.0	50.3 ± 1.9
150 min. after asphyxia		
Decreased MAP	49.8 ± 4.2	48.0 ± 2.1
Normal MAP	51.4 ± 3.2*	50.0 ± 2.2**
Elevated MAP	58.4 ± 4.2#	50.3 ± 2.4

* $p < 0.05$; ** $p < 0.01$ compared to CBF at normal MAP before asphyxia

# $p < 0.05$; ## $p < 0.01$ compared to CBF at normal MAP at the same time period

Title: **DOSE-RESPONSE RELATIONSHIP FOR VECURONIUM IN THE PRESENCE OF CHRONIC PHENYTOIN THERAPY**

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INTRODUCTION. Resistance to the neuromuscular blocking effects of the long acting relaxants in patients on chronic phenytoin therapy has been described for metocurine[1] and pancuronium[2]. This study was undertaken to determine whether or not a similar pharmacological interaction exists between phenytoin (DPH) and one of the intermediate acting neuromuscular blockers, vecuronium (Vc).

METHODS. This study was approved by the Institutional Review Board. Informed consent was obtained from a total of 34 neurosurgical patients (age 19 to 59); 17 of whom were on DPH therapy for at least one week prior to surgery (GROUP I), with the remaining 17 patients receiving no anticonvulsant therapy (GROUP II). Patients with abnormal liver or renal function, as well as those with neuromuscular dysfunction were excluded from this study. None of the patients exhibited obvious obesity. All patients were monitored and premedicated along standard departmental guidelines. For the first part of this study, 5 patients from each group were induced with thiopental 4-6 mg/kg, followed by moderate hyperventilation with N_2O 50% and halothane 1.0 to 1.5%, inspired, in oxygen. The ulnar nerve was stimulated at the wrist with 0.15 ms. supramaximal stimuli from a Grass S-8 stimulator at a rate of 0.1 Hz. The response was measured through the use of an FT-10 force displacement transducer. When the baseline response stabilized, a bolus of Vc 0.1mg/kg was given. With the appreciation of suitable relaxation lidocaine 1.0 - 1.5mg/kg was given and the trachea was intubated. Patients were ventilated to an end tidal CO_2 of 22 to 30mmHg with N_2O 50% and halothane 0.5 to 1.0%, inspired, in oxygen. The time from injection to maximum response (ONSET), times to recovery to 10,25,50,75 and 90% of baseline (T10,T25, etc.) and the recovery index (RI) defined as the time required to progress from 25 to 75% of baseline twitch (RI) were recorded. These parameters were compared between groups with Student's unpaired t-test. In the second part of this study, 12 patients in each group were given thiopental 3-5 mg/kg and ventilated by mask with N_2O 60% inspired in oxygen. Supplementary doses of thiopental 1mg/kg and/or fentanyl 0.001mg/kg were given as deemed neccessary. When the response to ulnar nerve stimulation was stable, patients received one of 3 preselected doses of Vc (0.03, 0.04 or 0.05 mg/kg in GROUP I; 0.02, 0.03 or 0.04 mg/kg in GROUP II). Recordings were made of the neuromuscular response until the maximum response was noted, at which time a second dose of Vc 0.1mg/kg was given to facilitate intubation. The maximum response for the various doses used in this part of the study was analyzed as log dose versus probility response using the method described by Litchfield and Wilcoxon[3]. The derived straight line dose-response relationships were compared between the two groups for goodness of fit (lack of heterogeneity), parallelism, potency ratio and Ed_{50}. Throughout this study,differences were considered significant if $P < 0.05$.

RESULTS. The response to a single Vc dose of 0.1mg/kg during halothane anesthesia is shown in Table 1. There is no difference in onset of neuromuscular blockade between the two groups. However, the recovery phase is markedly shortened in GROUP I. For example ,T50 is 22.7±5.1 min in GROUP I, compared to 50.5±10.1 min in GROUP II. Recovery appears to be at least twice as rapid in patients on chronic DPH therapy. This is confirmed by the large difference in RI seen between the two groups. The dose -response characteristics determined in the second part of this study are summarized in Table 2. The slopes of the derived straight line relationships are similar. For both lines, Chi square analysis revealed no significant heterogeneity. The deviation from parallelism between the two lines was not statistically significant. The potency ratio between GROUPS I and II was found to be 1.52 ($P<0.05$), with an ED_{50} of 0.041mg/kg and 0.027mg/kg respectively.

DISCUSSION. Resistence to the neuromuscular blocking effects of Vc in patients on chronic DPH therapy is demonstrated in this study. The results shown in the control group compare favorably with the results of other groups studying Vc dose-response during neurolept anesthesia with a single bolus method[4]. The DPH group is significantly different. Both the magnitude and duration of neuromuscular blockade fall short of that expected in the patient on chronic DPH. Although an alteration in the pharmacokinetics of elimination might be implicated on the basis of the different recovery indices, the presence of different dose-response relationships imply pharmacodynamic changes which could be verified by the generation of concentration vs. response curves.

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TABLE 1. Response in minutes to vecuronium 0.1mg/kg (mean ± s.d.). n = 5 in each group.

	GROUP I	GROUP II	P<
ONSET	3.8 ± 0.8	2.6 ± 1.1	NS
T10	16.0 ± 3.7	35.0 ± 5.2	0.001
T25	19.3 ± 4.3	41.9 ± 7.8	0.001
T50	22.7 ± 5.1	50.5 ± 10.1	0.001
T75	27.2 ± 6.0	59.6 ± 12.3	0.001
T90	31.9 ± 6.0	69.7 ± 12.9	0.001
RI	7.9 ± 2.2	17.8 ± 5.1	0.005

TABLE 2. Dose - response parameters with 95% confidence limits. n = 12 in each group

	GROUP I	GROUP II	P<
SLOPE	1.24 (0.95-1.61)	1.36 (0.98-1.89)	NS
ED_{50} (mg/kg)	0.041 (0.033-0.050)	0.027 (0.020-0.036)	0.05

Title: ANESTHETIC MANAGEMENT OF SYSTEMIC MASTOCYTOSIS: EXPERIENCE WITH 42 CASES

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Introduction. Systemic mastocytosis is characterized by pruritus, dermographia, syncope and cardiovascular collapse. Perioperatively, the disease state can be induced by extremes of temperature, emotional states and a number of pharmacological agents used in the course of a normal anesthetic, whether general or regional. The resulting cardiovascular collapse may be so profound and difficult to correct that death can result. In fact, several dramatic sudden deaths have occurred in our own clinic from this cause, but not during formal anesthesia. We have successfully administered anesthesia to 42 patients with a few reversible complications but no mortality.

Methods. Forty-two patients with clinical manifestations of systemic mastocytosis were admitted to our institution for a variety of surgical procedures. Definitive pre-operative laboratory diagnosis was made by skin biopsy and urine tests for the metabolite of prostaglandin D_2 in most cases (1). Intradermal skin tests were performed on all patients using (preservative free) normal saline as a control and each anesthetic agent that was planned for possible use during the anesthetic course (2). Skin tests were very useful in predicting the agent that may provoke exacerbation of mastocytosis. The size of the corresponding erythematous wheal indicated the approximate quantitative response to the respective agent.

Both regional and general anesthesia can produce life-threatening complications in mastocytosis patients undergoing surgical procedures. In an attempt to decrease the morbidity and mortality associated with this clinical syndrome, the following perioperative measures were adopted for the management of our patients:

1) Preoperative control with H_1 and H_2 histamine antagonists and non-steroidal anti-inflammatory agents (when possible).

2) The use of intradermal skin tests to predict the patients who may develop reactions to drugs that may be used electively or on an emergency basis if a complication develops.

3) The preopeative and postoperative (when applicable) determinations of urinary levels of the metabolite of prostaglandin D_2, serum prostaglandin F_2 alpha and skin biopsy.

4) Preoperative sedation with oral diazepam.

5) Administration of pre-induction dose of 25-50 mg diphenhydramine intravenously.

6) Continuous perioperative availability of epinephrine infusion (1 mg in 25 ml of normal saline) and epinephrine for bolus adminsitration (1:100,000). The dose used to manage acute exacerbation of systemic mastocytosis was 1-3 mg/kg intravenously.

7) The use of isoflurane for the induction (including the intubation of the trachea) and maintenance of general anesthesia.

8) The use of regional anesthesia when appropriate in order to minimize the number of pharmacological agents used for a given procedure.

Results. Table 1 shows that general anesthesia was administered more frequently than regional anesthesia (3.6:1). This was mainly due to the fact that the potent inhalational ether-linked anesthetics inhibit the degranulation of the mast cell (2). This effect of the inhalational agents appeared to be protective and beneficial. An analysis of the patients developing complications (mainly hypotensive and broncho-constriction episodes) shows that most of these complications were in patients having regional anesthesia.

TABLE 1: Clinical Data on Mastocytosis Patients

Number of patients with Mastocytosis	42
Age range	19-56 (yrs)
Mean Age	31 (yrs)
Female	40
Male	2
Patients receiving general anesthesia	33
Patients receiving regional anesthesia	9
Patients developing complications	6
Perioperative mortality	0
Patients requiring epinephrine infusion	5
Patients with positive skin tests	15

Discussion. The anesthetic management of systemic mastocytosis has always been associated with a high perioperative complication rate (3). We submit some recommendations for safe anesthetic administration of these patients. The use of H_1 and H_2 antagonists and non-steroidal anti-inflammatory agents is effective in the quiescent phase of mastocytosis but is totally ineffective in the acute stage. Intravenous infusion of epinephrine may be life-saving in acute exacerbation and should always be available during the perioperative management of these patients. Skin tests are useful in planning the anesthetic and in predicting the sensitivity of these patients to a variety of anesthetic agents. In the absence of coagulopathy there is a place for regional anesthesia with the amide-linked local anesthetics. Although mast cells themselves may release significant quantities of heparin (1), this was not a clinical problem in any of our cases. Finally, it should be stressed that acute exacerbation of systemic mastocytosis may be produced not only by some anesthetic agents but also by extremes of temperature, emotional stress and some food products.

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Supported by the Study Center for Anesthesia Toxicology, Vanderbilt University.

Title: EARLY DETECTION OF EXPERIMENTAL PULMONARY EDEMA IN SWINE

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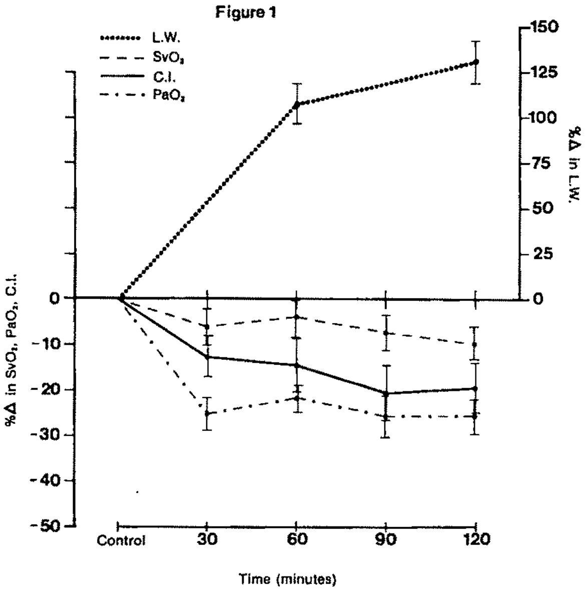
Introduction. It would be clinically useful to have a method of obtaining an early pathophysiologic indication of pulmonary edema in critically ill patients, so that appropriate therapy may be instituted before severe arterial hypoxemia or other problems develop. The fiberoptic infrared oxygen saturation monitoring PA catheter has made it clinically possible to continuously evaluate mixed venous oxygen saturation.[1] Additionally, a catheter to measure pulmonary extravascular lung water is also available.[2] This study was designed to compare the changes in arterial oxygen tension, extravascular lung water (EVLW), mixed venous oxygen saturation (SvO$_2$), and cardiac index (CI) in the experimental animal after ethchloroynol-induced pulmonary vascular damage.

Methods. Female swine weighing 40-50 kg (N = 15) were anesthetized with 1.5% halothane in 70% N_2/30% O_2. A tracheostomy was performed and mechanical ventilation instituted to achieve a $PaCO_2$ of 35-38 torr. A 20 gauge arterial catheter was inserted into the carotid artery; an Oximetrix 7.5 Fr fibroptic thermodilution catheter was passed via the right internal jugular vein into the pulmonary artery. An Edwards 96-020-5F femoral artery lung water catheter was inserted into the right femoral artery, and advanced into the abdominal aorta. After placement of monitoring catheters, two double indicator dilution estimates of EVLW were obtained using the method of Mihm, et al (2). Pulmonary edema was induced with a 20 mg/kg dose of ethchlorvynol given in two doses of 10 mg/kg with a 10 min interval between doses (3). Arterial and mixed venous blood gases were obtained every 10 min for the next two hours, and EVLW was measured by double indicator dilution each hour.

Data were analyzed with appropriately weighted t-tests for unpaired data. Differences were considered significant at the $P < 0.05$ level.

Results. The ethchlorvynol induced changes in Pa0$_2$, Sv0$_2$, EVLW, and CI are displayed in Fig 1 (data displayed as mean ± S.E.). Despite progressive increases in EVLW to 108% of control ($P < .0005$) at 60 min., and a further increase to 152% at control ($P < .0005$) at 120 min., there was little change in Sv0$_2$ until 90 min., and even then Sv0$_2$ decreased only 7.25% ($P < .05$), further decreasing to a 9.81% change at 120 min. ($P < .01$). This was true despite marked decreases in arterial oxygen tension and C.I.

Figure 1



Discussion. Sv0$_2$ did not markedly decrease despite decreases in Pa0$_2$ and C.I. Although this might have been due to decreased overall 0$_2$ demand, perhaps brought on by the ethchloroynol itself, nonetheless we could not demonstrate that Sv0$_2$ changes were early warnings of pulmonary edema.

We conclude: 1. EVLW and Pa0$_2$ are early indicators of experimental pulmonary damages; 2. Sv0$_2$ did not reflect early pulmonary damage. Measurement of EVLW, combined with arterial blood gases provided warnings of pulmonary edema in this experimental model.

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Title: *NALBUPHINE REVERSES EPIDURAL MORPHINE INDUCED RESPIRATORY DEPRESSION*

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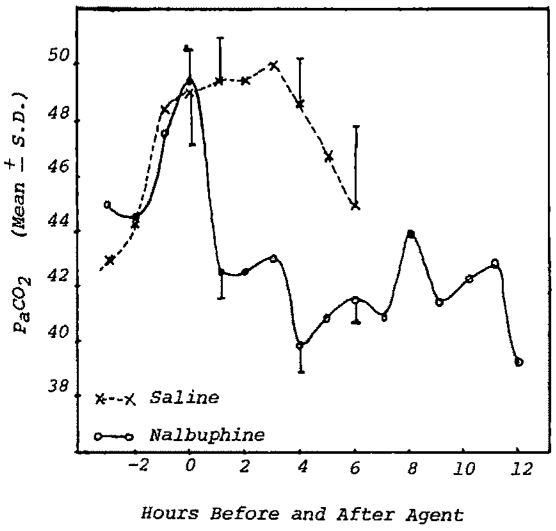
Introduction. Epidural morphine has become well recognized as an extremely effective means of providing post-operative analgesia. However, the associated problem of delayed respiratory depression has limited its use to intensive care areas. Nalbuphine is an agonist-antagonist narcotic with a serum half life ot two to four hours. This study was designed to evaluate nalbuphine's ability to reverse the respiratory depressant effect of epidural morphine and to assess it's effect on analgesia.

Methods. Following approval from the Institutional Ethics Committee, twenty pts., from whom written informed consents has been obtained, were studied. All were ASA-1 scheduled for elective TAH. The study was double blind, placebo controlled. Pre-med diazepam 5 mg po 1½ hr. pre-op, lumbar epidural catheter followed by test dose of 4 ml 2% Xylocaine - CO_2 with 1:200,000 epinephrine, epidural morphine 0.1 mg per kg. at induction, curare 3 mg - Pentothal 3-5 mg per kg - succinylcholine 1.5 mg per kg IV, endotracheal intubation and controlled ventilation, 70:30% $N_2O:O_2$ - isoflurane - curare, prostigmine and atropine 2.5:1.2 mg IV. One half hour post-op 0.05 mg per kg epidural morphine was given if required. Blood gases q2h. Five assessments of ventilatory response to CO_2, as described by Read, were performed in each patient: A to E. Initial test, A, was ½ hr. pre-op. Test B was six hours after the patient had received 0.1 mg per kg of epidural morphine at induction. Tests C,D and E sequentially followed B being spaced 20 minutes apart. The trial agent was given IV, 0.1 mg per kg, immediately upon completion of each of the tests B,C and D. The patient graded her pain according to a visual pain scale q2h plus before and after injection of trial agent.

Results. Fourteen patients received nalbuphine and 6 received saline. Ten patients had $PaCO_2$ greater than 45 torr at 6 hrs. after the 0.1 mg per kg epidural morphine. Six belonged to the nalbuphine group and four were from the saline group. The mean $PaCO_2$ values were derived for the two groups at the various times relative to agent administration. A t-test for two independant samples was performed at four time points: immediately prior to agent administration, one hour after agent, four hours and six hours after agent administration. The nalbuphine group experienced an 8 torr correction in $PaCO_2$ in the time interval from one to four hours after agent administration with a value for $p < 0.005$. Before agent administration and after four hours the two groups were statistically not different. Three saline patients required naloxone for $PaCO_2$ greater than 50 torr at various times after the saline administration. Assessment of ventilatory response to CO_2 will be reported in detail in a future publication. Patients who received saline had no improvement. An improved response was noted after 0.1 mg per kg nalbuphine. Further nalbuphine administration, up to 0.3 mg per mg., did not result in substantial gain. Not one patient reported a reversal of analgesia after 0.3 mg/kg nalbuphine.

Discussion. Nalbuphine antagonizes the respiratory depressant effects of epidural morphine but does not reverse analgesia. After 0.3 mg per kg, nalbuphine's protective effect appears to last at least four hours. Concurrent to an improved ventilatory response to CO_2 with nalbuphine, patients experienced a moderate increase in sedation. After 0.3 mg per kg,patients had a markedly decreased attention span so that many could not perform the CO_2 rebreathing test reliably. Therefore we conclude that although nalbuphine antagonizes respiratory depression, its sedative properties are additive to those of epidural morphine.

MEAN P_a CO_2 BEFORE AND AFTER AGENT



Title: EFFECT OF POSTOPERATIVE EPIDURAL ANALGESIA ON RESTING METABOLIC RATE (RMR) IN MAN

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Introduction. Epidural analgesia in the postoperative period has been shown to blunt or obliterate many of the facets of the metabolic response to surgery(1). In particular, following hysterectomy nitrogen balance was less negative(2), corticosteroids rose less(3), and catecholamines rose less(4). In contrast following total hip replacement no difference was found in resting oxygen consumption between patients epidural analgesia and patients receiving narcotic analgesia(5). We designed a study to address this apparent inconsistency and to answer the following questions: (a) Does continuous epidural analgesia effect postoperative metabolic rate as measured by resting oxygen consumption; and (b) Is the stress response to surgery as measured by urinary catecholamine excretion altered?

Methods. Following approval of the appropriate institutional review boards, and with the informed consent of the patients, the following study was undertaken. Patients - age 18 to 70, scheduled for elective total hip replacement, with no history of cardiac dysfunction, and who were not receiving hormonal supplementation - were admitted to the Clinical Research Center and randomized to one of two groups. One group (C) received subarachnoid anesthesia with tetracaine and postoperative narcotic analgesia (morphine sulfate 0.1 - 0.2mg/kg, i.m., q 2-4h prn), while the other group (E) received epidural bupivicaine anesthesia (0.5%) and postoperative epidural bupivicaine analgesia (0.2 - 0.375%) as a continuous infusion to maintain a sensory level at the tenth thoracic dermatome. RMR was measured by indirect calorimetry the morning of surgery and on postoperative days (POD) 1,2,& 3. Indirect calorimetry was measured using a ventilated hood system. Gas flow through the hood was adjusted to maintain a mixed expired carbon dioxide concentration of 0.5 to 1.0%. Mixed expired gases were continuously measured for flow (Vertek VR4500 pneumotachograph) oxygen content (Applied Electrochemistry S-3A fuel cell analyzer), and carbon dioxide content (Applied Electrochemistry infra-red analyzer CD-3A). Outputs were read every 6 seconds by a Hewlett-Packard 85 computer and mean values for $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and R.Q. (STPD) were calculated for each 5 minute collection period. Three periods were averaged for each measure of RMR. All urine was collected for the 72 hours following surgery and each 24h sample was analyzed for vanillylmandelic acid (VMA), metanephrines (MET), and total catecholamines (CAT) using high performance liquid chromatography with an electrochemical detector. Data were analyzed by analysis of variance.

Results. There were five patients in each group. The ages were similar for the two groups, 48 and 54 years for C and E respectively. Outcome parameters are charted on the following table: group differences for the postoperative period were significantly different for all four parameters measured, individual differences are noted on the legend.

		PRE-OP	POD 1	POD 2	POD 3
$\dot{V}_{O_2}$	E	132±10	143±6*	146±7*	144±6*
	C	131± 3	171±8	162±9	167±4
VMA	E		8.0±1.1	9.4±1.9	10.0±1.8
	C		10.8±1.2	13.2±2.2	11.4±2.9
MET	E		0.7±0.1*	0.9±0.1*	0.9±0.3
	C		1.2±0.1	1.3±0.2	1.0±0.1
CAT	E		99±13	99±21 *	106±16
	C		176±41	232±49	194±55

Data are presented as mean values ± S.E.M., VMA and MET are mg excreted per 24h, CAT is ug excreted per 24h.
*P 0.05.

Discussion. We conclude that postoperative epidural analgesia blunts the stress response to surgery as measured by resting oxygen consumption or catecholamine excretion. The postoperative oxygen consumption in our group receiving narcotic analgesia is virtually identicle to that of (5) for his narcotic group, thus the opposite findings of the two studies need to be explained. The differences between the two epidural groups are that he used lidocaine and we used bupivicaine and he allowed the epidurals to wear off intermittently to allow his patients to micturate while our analgesia was continuous and the patients bladders catheterized. Catecholamine infusions have been shown to increase RMR(5), and it is possible that the partial sympathectomy accompanying the epidural mediates the difference between the groups. Another possibolity is that the superior analgesia of the epidural is responsible for the difference. Regardless, following total hip replacement continuous epidural analgesia is associated with less of a rise of RMR thansystemic narcotic analgesia. If oxygen consumption correlates with cardiac output and cardiac work, then there may be a population of individualswith limited cardiac reserve who may benefit from epidural analgesia following surgery.

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Title: CEREBROVASCULAR EFFECTS OF RAPID FLUID RESUSCITATION IN A CANINE INTRACRANIAL MASS LESION MODEL

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Introduction: Cerebral blood flow (CBF) increases during isovolemic hemodilution with either crystalloid or colloid solution; in contrast, CBF does not increase during hemodilutional resuscitation from shock (1,2). In both situations, isotonic crystalloid solutions produce a higher intracranial pressure (ICP) than either colloid-containing or hypertonic crystalloid solutions (1,2). Consequently, we compared the effects on ICP, CBF, and cerebral oxygen transport (CO_2T) of resuscitation from hemorrhagic shock using 6% hetastarch (HS) or lactated Ringer's solution (RLS) in animals with an epidural mass lesion.

Methods: Thirteen 15- to 20-kg mongrel dogs were randomly selected to be resuscitated with HS or RLS. Dogs were anesthetized with pentobarbital, 30 mg/kg iv, paralyzed with iv succinylcholine, endotracheally intubated, and ventilated with tidal volumes of 15 ml/kg varied in frequency to regulate $PaCO_2$. A femoral artery catheter and pulmonary artery catheter were placed. The temporalis muscles were dissected from the skull, a subarachnoid bolt was placed to monitor ICP, an epidural balloon was placed through a burr hole, and a cadmium telluride scintillation probe was positioned over each parietal hemicranium for measurement of CBF by xenon-133 clearance. The epidural balloon was incrementally inflated with saline to maintain a stable ICP of 30 mmHg for 5 minutes. Blood was then withdrawn from the femoral artery catheter to produce and maintain a mean arterial pressure (MAP) of 55 mmHg for 30 minutes. Resuscitation was then performed with HS, 20 ml/kg, or RLS, 60 ml/kg iv, over 5 minutes. The following data were compared at baseline (BL), early shock (ES), late shock (LS), early resuscitation (ER), and late resuscitation (LR): ICP, CBF, CO_2T, MAP, cardiac output (CO), hemoglobin (Hgb), and pulmonary artery occlusion pressure (PAOP). Data were analyzed using multivariate analysis of variance with $p < 0.05$ being significant.

Results: Systemic Hemodynamics. MAP was similarly restored by both fluids. CO was significantly higher ($p < 0.05$) at ER in the RLS group, but declined rapidly, so that at LR there were no differences between the two groups.

Cerebral Hemodynamics. In the RLS group, ICP was significantly higher at ER ($p = 0.003$), and tended to be higher at LR ($p = 0.058$) (Fig.). CBF did not increase above LS levels in either group at ER and LR ($p < 0.05$). In both groups, CO_2T decreased during shock and then, due to hemodilution, decreased further at ER ($p < 0.05$ compared to LS values) and remained below LS values at LR ($p < 0.05$) (Fig.).

Discussion. In animals with intracranial mass lesions and hemorrhagic shock, resuscitation with HS produces a substantially lower ICP than does resuscitation with RLS. Restoration of MAP and CPP does not improve cerebral perfusion after hemorrhage in dogs with intracranial mass lesions. Colloid-containing solutions may be superior to RLS for resuscitation when hemorrhagic shock and intracranial mass lesions coexist.

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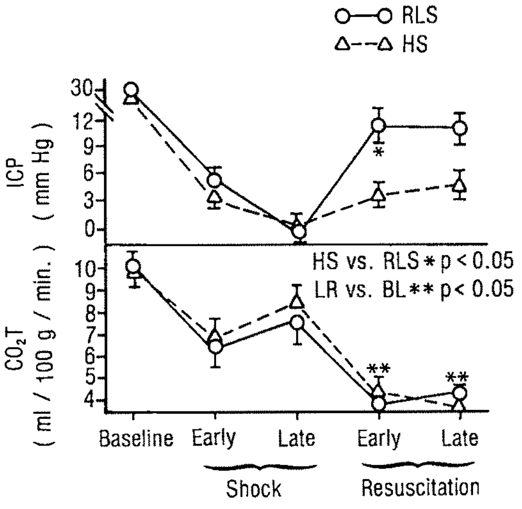

Title: INHIBITION OF THROMBOXANE A_2 PRODUCTION DOES NOT AFFECT POST-ISCHEMIC BRAIN HYPOPERFUSION IN DOGS

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Introduction. Post-ischemic brain hypoperfusion may increase neurological injury after relief of global brain ischemia; antagonism of post-ischemia hypoperfusion has been associated with less severe neurological injury (1). Thromboxane A_2 (TxA_2) is a powerful vasoconstrictor and platelet aggregatory substance synthesized from the arachidonate released from injured cell membranes (2). This study was performed to determine if systemic administration of a thromboxane synthetase inhibitor (TSI) before global brain ischemia would be associated with increased post-ischemic cerebral blood flow (CBF).

Materials and Methods: Twelve mongrel dogs weighing 15-25 kg were anesthetized with thiopental, 8-10 mg/kg iv, followed by succinylcholine, 1.5 mg/kg. Animals were endotracheally intubated and ventilated at an FIO_2 of 0.4 and a tidal volume of 15 ml/kg at a rate adjusted to produce a $PaCO_2$ of 35-45 mmHg. Halothane 1.0% in O_2 provided anesthesia for the placement of a femoral artery, a right pulmonary artery, and a retrograde internal jugular vein catheter followed by thoracotomy. The azygous vein was ligated, and the venae cavae and aorta were isolated and snares tied loosely around them. The temporalis muscles were dissected from the skull, and external cadmium telluride gamma detectors were positioned for determination of CBF by clearance of Xenon-133. Halothane was then discontinued and a 60:40 mixture of N_2O and O_2 was given for at least 30 minutes. Group I animals (n = 6) were controls; group II animals (n = 6) received a TSI (UK-38,485, 1.5 mg/kg iv). Baseline (BL) measurements included: CBF, mean arterial pressure (MAP), cardiac output (CO), pulmonary artery occlusion pressure, pH, $PaCO_2$ and PaO_2. Arterial and jugular venous blood samples were obtained for the determination of thromboxane B_2 (TxB_2), a stable metabolite of TxA_2. The aorta and venae cavae were occluded for 10 minutes. Blood for determination of TxB_2 levels was obtained immediately after unclamping (time 0) and at 10, 30, and 60 minutes after release of occlusion. TxB_2 levels were determined by radioimmunoassay. Hemodynamic variables and CBF were measured at times 0, 30, 60, 90, and 120 minutes.

Results: The figure displays changes in jugular venous TxB_2 levels and CBF in treated and untreated animals. Treated animals showed nearly complete inhibition of TxB_2 production. CBF in both groups was similar to baseline values at time 0, then declined similarly in both groups by 30 minutes to ≅ 40% of BL values where it remained thereafter. There were no significant differences in arterial blood gases, MAP, CO, filling pressures, or heart rate between the groups at any interval.

Discussion: Although large amounts of immunoreactive TxB_2, the major metabolite of TxA_2, are present in jugular venous blood following global brain ischemia, inhibiting systemic and cerebral TxA_2 production prior to global cerebral ischemia is not associated with improved post-ischemic CBF. We conclude that TxA_2 is not a major factor in the genesis of post-ischemic brain hypoperfusion, and that thromboxane synthetase inhibition is unlikely to improve neurological outcome after global brain ischemia.

This study was supported by the 1984 IARS research award.

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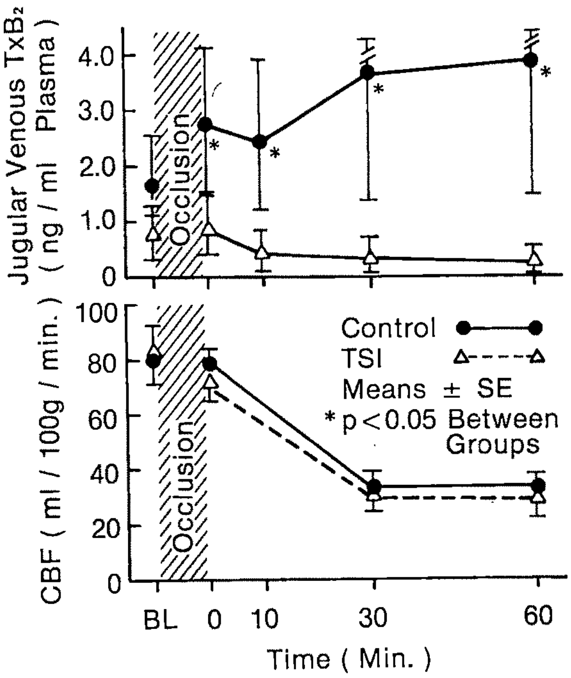

Title: PREMEDICATION ABOLISHES INCREASE IN PLASMA BETA-ENDORPHIN DUE TO PRE-SURGICAL STRESS

Authors: M. Puig, M.D., PhD, J. Walsh, M.D., C. Tang, M.D., M. Lovitz, B.S. and H. Turndorf, M.D.

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Introduction: A wide variety of central nervous system-active drugs are used for sedation and anxiolysis prior to surgery. A number of studies have examined patients' subjective perceptions, and independent observers' evaluations of pre-operative anxiety, as influenced by various premedication regimens.[1,2] Some of these studies attempted to standardize their methods of evaluation but most failed to reach complete objectivity. There is evidence that stress, emotional or physical, results in an increase in endogenous opioid activity, with increases in plasma beta-endorphin (B-END) levels. The objective of our study is to elicit data regarding the effects of premedication on a measureable physiologic parameter, namely, plasma concentrations of of B-END.

Methods: The research protocol was approved by the New York University Institutional Board of Research Associates for application to human subjects. Subjects were ASA PS I or II, taking no drugs (other than antibiotics) for 2 weeks prior to surgery. Patients were told that, as participants in the study, they would receive either no premedication, an oral (PO) or intramuscular (IM) placebo, or a PO or IM drug. Ten ml of venous blood was obtained at 4 PM on the day prior to surgery, and again on arrival in the operating room (8 AM) on the day of surgery. Approximately one hour prior to surgery, patients received (by random assignment) either no premedication, an IM placebo (saline), diazepam 10 mg PO, meperidine 1 mg/kg IM, or diphenhydramine 1 mg/kg IM. Blood specimens were also obtained from ten healthy volunteers, to serve as a control group. Plasma B-END was measured by radio-immuno assay. Analysis of variance (ANOVA) was applied to B-END (4 PM) and B-END (8 AM) groups. When ANOVA indicated a significant difference among groups, an unpaired t-test was used to compare individual premedication groups. A paired t-test was used to compare 4 PM and 8 AM values within each premedication group.

Results: Results are summarized in Fig. 1. There were no statistically significant differences in mean 4 PM B-END levels among all groups by ANOVA ($p > .1$) with an overall mean value of 4.09 pmol/l ± .26 (mean ± standard error). The control (non-surgical) group had an 8 AM mean of 4.29 ± .47, not significantly different from 4 PM values. Untreated surgical patients had significantly higher 8 AM levels (6.01 ± 1.61, $p < .05$). The placebo group showed no difference from untreated patients (5.98 ± .95, $p > .90$). Diazepam, diphenhydramine, and meperidine treated groups had significantly lower 8 AM mean B-END values than did unpremedicated patients (p values all $< .05$). The three premedication groups were not statistically different from each other. Paired t-tests demonstrated intra-group differences (4 PM vs 8 AM) to be significant only in the non-premedicated and placebo groups.

Discussion: There is a great amount of evidence in the literature indicating that stress results in increases in endogenous opioid activity, including plasma levels of B-END. Although most such experiments involve physical stress, a number of studies now show a similar physiologic response for emotional or psychological stress. In the belief that stress may be detrimental, at least in certain patients, the concept of stress-free anesthetic management has evolved[4], and has been recommended by some as a goal for optimal patient care. Our data suggests that the physiologic effects of stress begin in the pre-operative period, and that pharmacologic intervention at this time may be of aid in minimizing undesireable responses in the surgical patient.

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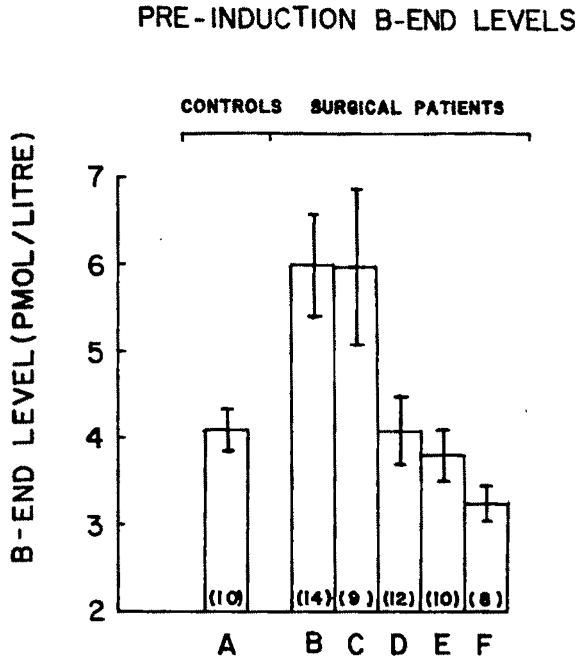

Fig. 1:
A = controls; B = no premedication; C = placebo; D = diazepem; E = diphenhydramine; F = meperidine. Parenthesis indicated number of subjects in each group. Columns indicate mean values; verticle bars = S.E.M.

Title: ANESTHETIC MANAGEMENT OF "HELLP SYNDROME" IN SEVERE PREECLAMPSIA-A RETROSPECTIVE STUDY

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INTRODUCTION-The term HELLP Syndrome was first coined by Louis Weinstein in 1981 (1). This describes the presence of hemolysis (H), elevated liver enzymes (EL) and low platelet count (LP) in patients with severe preeclampsia. This is now being recognized as a severe complication of the disease process and the cesarean section rate (C-Section) in this group is high ranging from 61.5-76%(2). The purpose of this report is to compare the maternal and neonatal outcome between patients receiving general and epidural anesthesia for C- Section in HELLP Syndrome.

METHODS AND MATERIALS-The charts of forty six patients with HELLP Syndrome who underwent C-Section in the last three years were reviewed. All patients had admission blood pressures of >160/110 torr, 2+ or 3+ proteinuria, generalised edema and epigastric pain. All received magnesium sulfate infusion and hydralazine as required. Laboratory data included hematocrit, coagulation profile, and serum electrolytes. Thirty patients received general anesthesia (GA) and sixteen patients received lumbar epidural anesthesia (LEA). All patients in the GA group were induced in the routine manner with pentothal and succinyl choline and anesthesia was maintained with either enflurane or isoflurane 0.5-1%. In the LEA group, the epidural catheter was inserted in the usual manner at the L$_{3-4}$ interspace and a T$_{4-6}$ level of anesthesia was achieved using 18-20 ccs of either 3% nesecaine or 2% lidocaine. The statistical analysis was performed using Student's t-test and chi-square analysis and a p value less than 0.05 was considered significant.

RESULTS-The two groups were similar in age, height, weight, parity and gestational age. There were no significant differences in the blood loss or fluids administered during the procedure between the two groups. The preoperative and postoperative PT, PTT and fibrinogen levels were normal in all patients except one patient in the GA group. The bleeding times were not determined in any patient preoperatively. The platelet counts decreased significantly in both groups in the immediate postpartum period (see Table 1). The number of babies with apgar scores <7 at 1 minute (21/30) was significantly higher in the GA group than in the LEA group (5/16) (p<0.01) which was probably related to the lower birthweight in the GA Group (1609.67±783.59 Gm) when compared to LEA group (2198.75±1070.03 Gm) (P<0.03). Post operative complications in the GA group included one maternal death due to DIC and ARDS. In the LEA group, one patient developed bleeding from gums, incision sites, iv sites, epidural insertion site and hematuria. The platelet count in this patient decreased from 125,000/mm^3 to 64,000/mm^3. The epidural catheter was left in situ until the platelet count was corrected. There was no evidence of epidural hematoma.

DISCUSSION-In HELLP syndrome severe thrombocytopenia may be present in the absence of other coagulation defects. Progressive worsening of the condition may occur during the course of management (2). It is well known that in severe preeclampsia the hypertensive response to endotracheal intubation during C-section can cause cardiac arrhythmias and cerebral hemmorage.(3) The presence of thrombocytopenia further increases the risk. In the absence of other major coagulation defects, when the platelet count was well above 100,000/mm^3 lumbar epidural anesthesia was chosen for these patients. However, there is a tendency for significant reduction in the platelet count in the intra operative and postpartum period in these patients in the absence of other coagulation abnormalities. Determination of bleeding times would have been helpful. The findings of this retrospective study suggests that in patients with HELLP Syndrome if lumbar epidural anesthesia is administered serial determinations of the bleeding time and platelet count are necessary as significant thrombocytopenia may develop during the course of the anesthetic management and this may occur in the absence of other major coagulation defects.

Table 1 Comparison of Platelet Counts (N/mm^3) between pre-operative and post-partum periods.

	Pre-operative	-	Post-partum (Lowest)	p
1) LEA (n=16)	131.3±44.4,000	-	71.4±24.1,000	<0.006
2) GA (n=30)	89.7±40.2,000	-	53.8±23.1,000	<0.0008

Values are given as mean ± SD

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Title: CARDIAC PRELOAD CHANGES WITH EPHEDRINE THERAPY FOR HYPOTENSION IN OBSTETRICAL PATIENTS

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Introduction: Ephedrine is used for treating maternal hypotension due to lumbar epidural anesthesia (LEA). Ephedrine is believed to correct blood pressure mainly by cardiac stimulation. However, there are no human data to verify this. This study assesses this effect of Ephedrine therapy on ventricular stroke volume (SV), ejection fraction (EF) and preload in patients scheduled to undergo elective cesarean section under LEA.

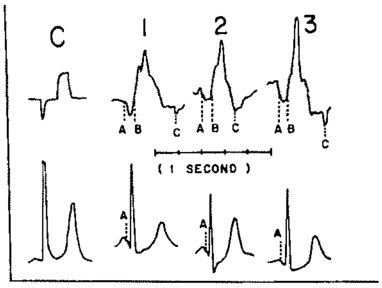
Methods: The study was approved by the review committee. Informed consent was obtained. 40 healthy patients (age 31±5, weight 73±6 kg) carrying an uncomplicated term gestation were studied. Systolic time intervals: preejection period (PEP) and ventricular ejection time (VET) were measured non-invasively using an impedance cardiograph (Instrumentation for Medicine). The first derivative impedance cardiogram (dz/dt trace) was obtained using the 4 sets of adhesive electrodes in the recommended anatomic sites. EKG was recorded continuously. All recordings were made on a Gould recorder at 50 mm/sec. PEP was measured from the onset of Q-wave of the EKG to the onset of ventricuular ejection on the dz/dt trace[1,2] (Fig 1). VET was measured from the onset of ventricular ejection to the lowest point of the dz/dt tracing. SV was calculated by using Kubicek's formula.[1] EF was calculated using Garrad's formula:[2] EF = 1.125 -1.250 x PEP/LVET. Ventricular EDV (preload) was calculated from the equation: EDV=SV/EF. Following an intravenous infusion of 1200 ml of Ringers lactate, LEA was induced to T_6 level by injecting lidocaine 1.5% under Ephedrine 1:200,000 at 5 ml increments. Left uterine displacement was maintained. Systemic pressure was measured every minute and ephedrine was administered in 5 mg increments to correct any systolic pressure less than 100 torr. Results were expressed as mean 1±1 SE and analyzed using t test at $p<0.05$.

Results: Twenty eight patients required no vasopressor (control) and 12 required 2±0.3 injections of ephedrine. In control subjects HR increased significantly after induction of LEA but mean blood pressure ($\overline{BP}$) did not change from baseline at T_{10} or T_6 level. VET, EF and PEP decreased significantly at T_6 level compared to preinduction values (Table). SV, cardiac output (CO) and EDV did not change significantly. In those who required ephedrine HR increased when $\overline{BP}$ decreased but PEP, VET, EF, SV, CO and EDV decreased (Table and Fig 2). Ephedrine decreased the HR but increased EF, PEP, VET, SV, CO and EDV significantly from those obtained during hypotensive period. Post-ephedrine EF, PEP and EDV were not different from preinduction values. CO was greater than preinduction value but VET was less.

Discussion: Data show that in those who did not become hypotensive SV, EDV and CO were maintained. Hypotension due to regional anesthesia is associated with decreased SV, EDV and EF. Decreased EDV may be due to lack of cardiac preload resulting from venous pooling. Decreased EDV also shortens VET. Ephedrine restores preload probably by constricting the capacitance bed. After ephedrine therapy EDV increased 34% but and only 12%. Increased arteriolar vaso constriction without a change in preload usually decreases the SV. Because SV increased with ephedrine, its mechanism of action seems mainly due to its ability to increase preload and not due to increased afterload. The decrease in HR after Ephedrine may be due to the baroceptor reflex.

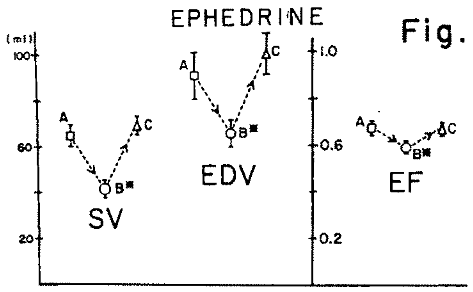
			CONTROL	(n=28, $\bar{x}$ ± (1SE))				
	HR (/min)	$\overline{BP}$ (torr)	VET (sec)	PEP (sec)	EF	SV (ml)	EDV (ml)	CO (1/min)
Base	80	90	0.32	0.08	0.65	69	108	5.5
line	(2)	(3)	-----	0.01	-----	(5)	(9)	(0.3)
T10	87	88	0.31	0.08	0.63	67	107	5.9
	(6)	(3)	-----	0.01	-----	(4)	(9)	(0.5)
T6	98	89	0.28	0.07	0.65	62	101	5.9
	(5)	(3)	-----	0.01	-----	(5)	(9)	(0.5)
			EPHEDRINE	(n= 12)				
Base	79	90	0.32	0.07				5.1
line	(3)	(3)	-- 0.01 ---					(0.3)
Hypo	107	67	0.19	0.06	See Figure			4.3
tension	(5)	(2)	-- 0.01 ---					(0.4)
Post	87	87	0.28	0.07				5.8
ephedrine	(10)	(3)	-- 0.01 ---					(0.39)

Fig. I



Legend for Fig 1: C-calibration 1 ohm.sec; 1, baseline; 2,hypotension; and 3 after ephedrine. A, onset of Q wave; B, onset of ventricular ejection; C end of ejection.

Fig. 2



Legend for figure A = preinduction;B=preephedrine; C = postephedrine.* - significantly different from A and C.

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TITLE: ACQUIRED IMMUNE DEFICIENCY SYNDROME AND ANESTHESIA PERSONNEL

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Introduction. Transfusion associated with Acquired Immune Deficiency Syndrome (AIDS) is increasing steadily. Chances for the possibility of health care workers contracting AIDS, either by direct contact or from blood and blood products, intensifies as the magnitude of the AIDS epidemic increases. By April, 1985 there were 9,319 reported cases of AIDS in the United States, 3,282 cases having been reported from New York City. Of the latter there were 23 cases associated with blood and blood products. Transfusion associated AIDS (TRAIDS) occurred in hemophiliacs and in patients receiving large numbers (¨10 units) of blood transfusions.

In an effort to determine the degree of exposure of Memorial Hospital operative and recovery personnel to the AIDS patient, a review of surgical procedures was undertaken.

Method. All patients treated at Memorial Hospital from 1981 to 1984 with the diagnosis of AIDS were reviewed. Group I consisted of adult patients with a definitive diagnosis of AIDS. Group II encompassed children with AIDS. Also reviewed were homosexual men with Kaposi's Sarcoma which formulated Group III and homosexual men with lymphadenopathy as Group IV.

Each group was studied (1) for its total number of patients; (2) for the number within each group that required operative procedures; and, (3) for the total number of operative interventions. Groups were also compared against each other.

Results. Our total review consisted of 495 patients treated at Memorial Sloan-Kettering Cancer Center between 1981 and 1984. Eighty-six of these patients required surgical treatment in the operating room. Due to the nature of the disease, many of these patients require multiple surgical procedures. These same 86 patients have undergone 111 surgical procedures during this time period. Operations ranged from diagnostic lymph node biopsy to extensive surgical procedures.

Table I

	GR I	GR II	GR III	GR IV
Number of Patients	71	5	236	184
Patients requiring surgical procedures	12	4	42	28
Lost to follow-up	2	0	4	2
Number of surgical procedures	15	7	53	36

Table II -

	GR I	GR II	GR III	GR IV
Operations				
1981	1	0	3	1
1982	2	0	13	10
1983	9	2	19	12
1984	3	5	18	13

Statistical analysis of the data will be presented.

Discussion. Because hepatitis B virus serologic markers are elevated in anesthesia personnel (18.8% in a recent study)[1] and because TRAIDS is transmitted in a manner similar to hepatitis B the possibility arises that anesthesia personnel could be at risk to contract TRAIDS. An added complication is the fear that hepatitis B vaccine might be contaminated by HTLV III because it is manufactured from pooled plasma.

An ongoing study by the Centers for Disease Control has found no cases of HTLV-III infections in exposed health care workers (HCW). Studies on "needle sticks" in 52 HCW showed no seropositive HTLV-III. In another study none of 188 HCW working with AIDS patients or their specimens was positive for HTLV-III. Finally there is one reported case in which hepatitis B was transmitted to a HCW without transmission of AIDS after a needle stick while treating a patient with both hepatitis B and AIDS. However, it must be remembered that a definitive incubation period of AIDS has not been determined. In addition the Centers for Disease Control has found no evidence for transmission of AIDS by hepatitis B vaccine. Many of the HCW with exposure to AIDS are continuing to be monitored in an effort to detect seroconversion to HTLV-III.

The present philosophy in regard to infection is that the isolation procedure currently recommended for AIDS are adequate and that the rate of transmission within hospitals is low. At Memorial Sloan-Kettering Cancer Center the isolation procedures are those for patients on hepatitis, enteric and pulmonary precautions.

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TITLE: OPERATIVE PROCEDURES ASSOCIATED WITH THE ACQUIRED IMMUNE DEFICIENCY SYNDROME COMPLEX

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Introduction. The anesthesiologists must be aware of the medical problems of all surgical patients. This is particularly important for the AIDS patient as the immunosuppression of AIDS adversely affects many organ systems. The social implications of AIDS can alter routine management and AIDS patients are often not presented as such.

In an effort to determine more about the AIDS patient and his operative experience and to alert anesthesia personnel to those procedures involving AIDS patients, AIDS patients treated at Memorial Hospital throughout a four-year period were studied. Also considered were homosexual men with Kaposi's Sarcoma and homosexual men with lymphadenopathy.

Method. These criteria applied to 496 patients treated at Memorial Hospital from 1981-1984. Those patients who required a surgical procedure were reviewed. Group I consisted of adults with a diagnosis of AIDS while Group II were children. Group III contained homosexual men with Kaposi's Sarcoma. Group IV were homosexual men with lympadenopathy.

Within each group, the number of patients that required a surgical procedure and the number that required multiple surgical interventions were determined and compared to the total group. Surgical procedures were studied with regard to number, typed within each group and compared against each other.

Results.

Table I

	GR I	GR II	GR III	GR IV
Total No. of patients	71	5	236	184
No. of patients requiring surgery	12	4	42	28
Lost to follow-up	2	0	4	2
No. of patients requiring multiple procedures	4	3	8	4

Table II

	GR I	GR II	GR III	GR IV
Types of procedures:				
-biopsy only (periph)	5	7	31	21
-biopsy only (major)	1	0	2	0
-insertion vascular access catheter	2	4	12	4
-excision fistula/ abscess	3	0	2	1
-other	4	0	7	10
-related to disease	3	0	7	9
-unrelated	1	0	0	1

Discussion.

The Anesthesiologist must be cognizant of patients who might have AIDS. When anesthesia is administered to patients of questionable sexuality, drug addiction or hemophiliacs who show evidence of weight loss and inanition, the possibility of AIDS should be considered.

Not only can the classical AIDS syndrome occur but also homosexual men with lymphadenopathy and those with Kaposi's syndrome are at risk for infectivity. The diagnosis of AIDS is made by a history of fever for longer than 3 months, chronic diarrhea, fatigue, night sweats, reduced number of Helper T cells, a diminished Helper/suppressor T cell ratio, decreased lymphoproliferative responses and increased serum globulins. A patient that does not have the AIDS syndrome does not mean that he will not develop it or that at the present time we have sufficient immunologic evidence to rule out the infectiveness of these conditions.

Testing for the human T-cell lymphotropic virus is just beginning and the social, ethical and medical consequences of reportability of a positive result is just being evaluated. Thus a patient may have a positive test for HTLV-III virus and the results not be entered in the patients chart or admitted to by the patient.

Our results indicate that the majority of these patients present to the operating room for peripheral biopsies and the insertion of vascular access catheters. Such patients who also meet the above criteria should be considered to be at risk for a positive HTLV-III antibody test and be handled as infectious.

Additionally, enteric, hepatic and pulmonary precautions should be taken since these patients are the victims of opportunistic infections and are at risk to transmit them.

It should be remembered that other general surgical procedures, often related to these diseases, are required. Routine anesthetic management must be coupled with the superimposing risks of the immunosuppressed patients.

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Title: PLANNING ANESTHESIA SERVICES TO SUPPORT EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY

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Introduction. Extracorporeal Shockwave Lithotripsy (ESWL) has been introduced into medical practice in the U.S. as a revolutionary method for the noninvasive destruction of kidney stones. The Dornier ESWL device is being applied clinically in this country and is designed to produce a high energy shock wave external to a patient who is positioned in a semi-reclining position in a tank of water. By means of an ellipsoidal reflector, this energy is brought to focus on renal calculi within the renal collecting system. After 1500-2000 shockwaves (triggered by the R wave of the ECG), the stones are reduced to particles that then can be passed in the urine, thereby obviating the need for an open surgical procedure. Our Department of Anesthesiology was involved from the outset in planning the construction of the facility and in implementing a program to provide anesthesia services for this group of patients. This report will describe the characteristics of our anesthetic practice during the first three months this facility was in use. Current projections are for 50 to 100 more of these facilities to be established throughout the U.S. within the next two years. Our experience has implications for the planning, construction and operation of ESWL units.

Methods. We began treating patients in late 1984 and collected data related to the anesthetic care of these patients from the outset. This included general information describing the patients as well as information more specifically reporting anesthetic conduct (technique, drugs, recovery characteristics) and course of the ESWL treatment (duration of treatment, multiple or bilateral stones, need for retreatment). This study was conducted entirely during the course of the FDA evaluation of the technique. The FDA protocol was approved by the institution's Human Investigation Committee and required patients to be ASA Physical Status I or II, to have small stones in either kidney (although multiple small stones were accepted for treatment), and to be uninfected. Lithotripsy centers in Germany had conducted these procedures under both epidural and general anesthesia (1). Our program was begun with a bias heavily in favor of using epidural as the principal means of anesthesia.

Results. Of 164 treatments during 65 working days, 29 were in patients treated previously. There was a progressive increase in the number of patients treated per day. The average age and weight (±S.D.) of our patients was 48 ± 3 years and 80.5 ± 16.8 kg. The primary anesthetic technique for these ESWL treatments was continuous epidural anesthesia in 133 instances, general anesthesia in 13, and subarachnoid block (SAB) in 7. In addition, unsatisfactory regional anesthetics were converted to general anesthetics in 6 instances and attempted epidurals were converted to SAB's in 4. There was one continuous SAB. There were three post-anesthetic headaches reported, all after SAB's including the continuous SAB. There were no major post-anesthetic complications. The following stone characteristics were seen:

DESCRIPTION OF STONES

	Single	Multiple	Fragments
Left	53	19	6
Right	30	19	4
Bilateral	6	26	---

EXTENSIONS OF TREATMENT

	NUMBER	PER CENT
BILATERAL ESWL TREATMENT	18	11.0%
ENDOSCOPY PRIOR TO ESWL Rx	31	19.4%
REPEAT TREATMENTS	29	17.7%

TIME IN RECOVERY UNIT

	--- MINUTES (N=164) ---	
	MODE	MEAN
ALL PATIENTS	70	90
EPIDURAL (N=133)	70	85
GENERAL (N=19)	70	91
SAB (N=12)	150	138

Discussion. In order to maximize the use of the ESWL device we planned and constructed a room adjacent to the lithotripter treatment room to be available for patient preparation and anesthesia. At our institution it was not possible to develop the ESWL facility adjacent to the main operating suite where the majority of anesthetic practice occurs. Because of this, we needed to assure the availability of a sufficient number of cases requiring anesthesia services to justify the assignment of Anesthesia Department staff to the area. Therefore, the facility was designed to include two G.U. endoscopy rooms outfitted for anesthetic administration. In addition to performing a large fraction of the anesthetics provided to G.U. patients in this area, we have found that 19% of our ESWL patients require an endourologic procedure, usually involving ureteral instrumentation, to dislodge fragments, to relieve ureteral obstruction or to prepare for ESWL using contrast material instilled into the renal pelvis. Fluoroscopy is necessary for these procedures and we recommend that an endoscopic room near the ESWL device be so equipped. Daily operation of the facility regularly involves anesthesia care of patients in the Anesthesia 'Induction/Preparation' room, the ESWL treatment room and one of the G.U. endoscopy rooms. We have included a six-bed post-anesthesia care unit (PACU) in the facility. Patients cared for here are returned to their hospital rooms following anesthetic recovery. At the end of the day after the last ESWL treatment is completed, the attending anesthesiologist and the PACU nursing staff may elect to transfer patients to the main PACU.

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Title: PHARMACOKINETICS OF ALFENTANIL IN CHILDREN

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Introduction. The age-related pharmacokinetics of alfentanil have not been studied in children. Meistelman et al[1] demonstrated that children aged 5 to 8 years have a decrease in the Vdss, the volume of distribution, and as a result, a shortening of the t ½ beta (the elimination half-life). The aim of this study was to determine whether pharmacokinetics varied with age or weight of the normal pediatric patient, and also the dosage of the drug given at 2 commonly-recommended doses.

Methods. This study was approved by the Joint Committee on Medical Bioethics of the University of Calgary; consent for inclusion in the study was obtained from all parents. With no premedication, 3 groups of ASA I patients were studied. Group I was aged 3-12 months and Group II aged 12 months to 14 years. Both groups received alfentanil 50 micrograms/kg. Group III, aged 14 months to 14 years received alfentanil 120 micrograms/kg. Patients had a variety of surgical procedures performed, receiving an inhalational induction of anaesthesia with halothane and nitrous oxide/oxygen, followed by a bolus of pancuronium 0.1 mg/kg, and endotracheal intubation. With a maintenance anaesthetic of 0.5% halothane in nitrous oxide/oxygen, a single intravenous bolus of alfentanil was given. Over the next 6 hours, 14 blood samples were drawn and alfentanil concentrations measured in triplicate by radioimmunassay. The accuracy and reproducibility of the assay was calculated by determining the alfentanil concentration in 7 blank plasma samples spiked with alfentanil in the concentration range of 0.2-600 nanograms/ml. The measured alfentanil concentration was within 6% of the calculated concentration for all samples, with a coefficient of variation of 4% or less (n=25). Initial estimates of the pharmacokinetic parameters were calculated with the curve-stripping program described by Naizi[2], using a Hewlett Packard computer. Concentration/time points of alfentanil were best fitted to a two-compartment model using the Non-Lin computer program.

Results. Table I summarizes the pharmacokinetic data from all 18 patients.

Discussion. Our results show that Vdss is half that found in adults and clearance rate is slightly faster[3], both of which contribute to the shorter t ½ beta, as t ½ beta = 0.693 x Vdss/clearance. They suggest, in addition, that alfentanil pharmacokinetics have no correlation with age (or weight) in pediatric patients aged 3 months to 14 years and they are dose independant. Because there was no difference in pharmacokinetic results between the doses of alfentanil administered, it would appear that there is no saturation of metabolic processes in doses up to 120 micrograms/kg. In comparing our results for alfentanil with age-related studies which have been done for other drugs (e.g. fentanyl, theophylline, phenytoin), it might be assumed that the difference in pharmacokinetics would be a reflection of increased metabolic rate in pediatric patients. It is possible, however, that the difference we have observed could be methodological. As a result of our studies, it might be expected that in pediatric patients blood levels would be higher for an equivalent dose/kg and a faster decrease in blood levels would occur. It is conceivable that the duration of action of alfentanil may be shorter than in adults.

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TABLE I. Pharmacokinetic data comparison for 18 patients aged 3 months to 14 years with adult data. Doses are 50 and 120 micrograms/kg.

	Our Results	Adults
T.B.C.	7.99 (1.75)	6.4 (1.4) ml/kg/min
Vdss	530 (238)	860 (940) ml/kg
t ½ alpha	12 (4.4)	11.6 (1.6) minutes
t ½ beta	68.27 (22)	94 (1.9) minutes

TABLE II. Pharmacokinetic comparison between groups.

	Group I	Group II
Number	6	7
Age	3-12 months	1-14 years
Vc	168 (58)	208 (37)
T.B.C.	7.9 (1.15)	7.9 (2.2)
Vdss	471 (227)	509 (197)
t ½ alpha	9 (5.6)	13.7 (2.8)
t ½ beta	70 (23)	83 (37)

Where.: Values are mean (Standard Deviation)

Vc = volume of central compartment
T.B.C. = total body clearance
Vdss = volume of distribution
t ½ alpha = distribution phase half-life
t ½ beta = elimination phase half-life

TITLE: DIFFERENTIAL EFFECTS OF ISOFLURANE ON HUMAN CENTRAL NERVOUS SYSTEM STUDIED BY MEDIAN NERVE EVOKED POTENTIALS

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Introduction: Intraoperative somato-sensory evoked potentials (SSEPs) have been increasingly used in recent years to monitor neurological function in patients undergoing scoliosis surgery and other neurosurgical procedures. Knowledge of the effect of anesthetics being used, on SSEPs therefore has obvious significance in the management of these patients. The present investigation was undertaken to study the effects of clinically used concentrations of isoflurane on different components of median nerve somatosensory evoked potentials (MN-SSEPs).

Methods: Institutional approval of the study protocol was obtained. Fifteen consenting adult patients (ASA Class I) were studied. Preoperatively MN-SSEPs were recorded. Anesthesia was induced with intravenous thiamylal sodium (3-7 mg/kg) followed by either succinylcholine (1 mg/kg) or pancuronium bromide (0.1 mg/kg) to facilitate endotracheal intubation. Heart rate, EKG, systemic blood pressure, esophageal temperature, and end tidal concentrations of carbon dioxide and isoflurane were continuously monitored during surgery. Anesthesia was maintained with oxygen and isoflurane. Median nerve somato-sensory evoked potentials were recorded at 0.5, 1, 1.5 and 2 percent end tidal isoflurane concentrations. Recordings of MN-SSEPs began at least 20 min after injection of thiamylal sodium and end tidal isoflurane concentrations were held constant for at least 10 min before recordings. Order of exposure to different isoflurane concentrations varied among patients. The dose of isoflurane was administered according to needs of the patient in keeping with the level of surgical stimulation. Therefore, not all patients could be studied at all concentrations of isoflurane. We could record MN-SSEPs at stable end tidal isoflurane concentrations of 0.5% in seven, 1.0% in all fifteen, 1.5% in fourteen, and 2% in ten patients. Thirteen out of fifteen patients were successfully studied at both 1% and 1.5% concentrations.

Stimulation and recording parameters for MN-SSEPs followed the American Encephalographic Society guidelines[1]. Absolute latencies and amplitude of Erb's point potential (EP), cervical potential (N13), and scalp potential (N20) were measured. From these values conduction times from EP to N13, N13 to N20, and EP to N20 were calculated.

Statistical Analysis: Numerical data were subjected to repeated measures analysis of variance using Hotelling's T-square test to determine statistical significance. A p-value less than 0.05 was considered significant. Values obtained in thirteen patients which could be studied at both 1.0% and 1.5% end tidal isoflurane concentrations were included for repeated measured analysis of variance.

Results: Erb's potential (EP) and N13 latencies increased slightly at all concentrations but these waves remained well defined. Contralateral scalp responses (N20) were reduced in amplitude but were evident in all patients after end tidal concentrations of 0.5 and 1.0 percent, in thirteen out of fourteen patients after 1.5% and in seven out of ten patients after 2% isoflurane. Both prolongation of latency of N20 and increase in conduction time from EP to N20 were dose related. Mean increase in latency of N20 in seven patients after 2% isoflurane was 3.71 msec. The range being 2.07 to 5.04 msec. Mean EP - N20 conduction time increased by 3.23 msec with a range of 1.71 to 4.40 msec. Components later than N20 were less durable and could not be identified after more than 0.5% isoflurane. Mean values for absolute latencies of different peaks and interpeak conduction times at various end tidal concentrations studied are shown in Tables 1 and 2 respectively. Absolute latencies of EP, N13 and N20 increased significantly when compared with control values. The difference between latencies of EP and N13 recorded after administration of 1% and 1.5% isoflurane was not significant (not dose-related), while that for latency of N20 was significant. There was no significant change in conduction time from EP to N13 at any concentration of isoflurane studied while conduction time from N13 to N20 increased significantly with the administration of isoflurane compared to control values. The difference in N13 - N20 conduction time recorded at 1% and 1.5% concentrations of isoflurane was also significant.

Discussion: Our findings suggest that intraoperative MN-SSEPs monitoring with isoflurane anesthesia is often feasible. Isoflurane has differential effect on potentials generated at different levels of the nervous system. Potentials generated in rostral somatosensory pathway (N18, N20, P23, etc.) are increasingly attenuated. Peripheral nerve, cervical spinal cord and caudal brainstem are minimally effected. The durable N13-P14 potentials may be the most suitable of the MN-SSEPs for intraoperative monitoring when isoflurane is the anesthetic being used. N20 is preserved but is markedly attenuated at end tidal concentrations of 2% isoflurane. These findings lead us to conclude that isoflurane may alter synaptic transmission more than afferent fiber conduction in central somato-sensory pathways.

References
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TABLE 1
Absolute Latencies and Conduction Times (Mean ± S.D.) of Different Peaks of MN-SSEPs at Different Concentrations of Isoflurane

End Tidal Isoflurane Conc.	N	Absolute Latencies			Conduction Times		
		EP	N13	N20	EP - N13	N13 - N20	EP - N20
Control	15	10.41 ± 79*	13.78 ± .91*	19.34 ± 1.39*	3.65 ± .38*	5.54 ± 1.83*	9.19 ± 1.01*
0.5%	7	11.22 ± .98	12.93 ± 5.51	21.66 ± 1.95	3.55 ± 1.46	6.88 ± 1.32	10.44 ± 2.00
1.0%	15	10.73 ± 85*	14.49 ± 1.42*	21.95 ± 2.08*	3.76 ± .73*	7.46 ± 1.60*	11.22 ± 1.65*
1.5%	14	10.73 ± .76*	14.49 ± 1.42*	22.94 ± 1.73*	3.77 ± .69*	8.37 ± 1.50*	12.14 ± 1.56*
2.0%	10	10.32 ± .74	14.26 ± 1.26	22.85 ± .66	3.94 ± .74	9.01 ± .72	12.68 ± .58
P-value	13	.0003	.0356	.0000	.73	.0000	.0000

*Values included in repeated measures analysis of variance

Pairwise Comparisons:

	EP	N13	N20	EP - N13	N13 - N20	EP - N20
Control vs 1%	Significant	Significant	Significant	N.S.	Significant	Significant
Control vs 1.5%	Significant	Significant	Significant	N.S.	Significant	Significant
1% vs 1.5%	N.S.	N.S.	Significant	N.S.	Significant	Significant

Title: HYPERKALEMIA AFTER DANTROLENE ADMINISTRATION IN DOGS

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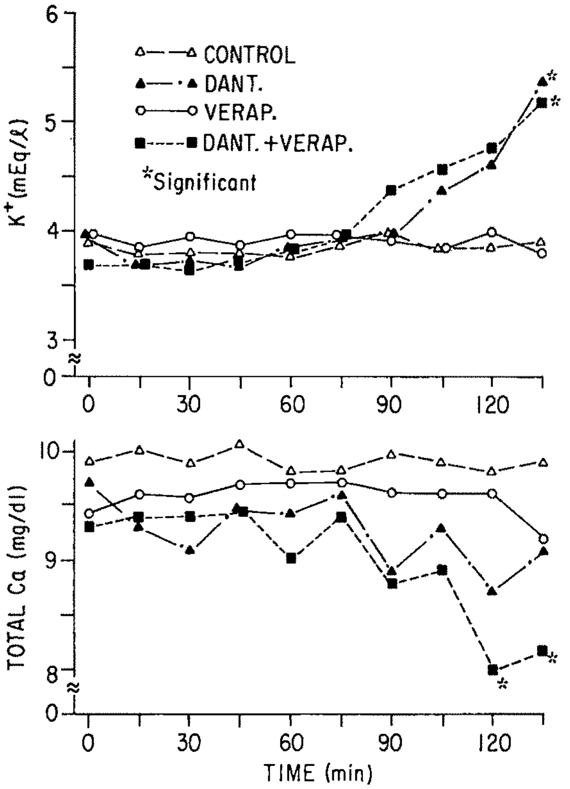
Introduction. Dantrolene in the presence of verapamil has been reported to cause cardiovascular depression in dogs[1] and to cause hyperkalemia and cardiovascular collapse in pigs.[2] It is unclear whether the response in pigs is species-specific. Serum sodium, potassium, calcium (ionized and total) and osmolality (OSM) have not been examined in the dog model. We therefore measured the above and the cardiovascular parameters in dogs given dantrolene with and without concurrent verapamil administration.

Methods. Twenty mongrel dogs, weighing 14-21 kg, were induced by sodium thiopenthal (20 mg/kg, IV), intubated and mechanically ventilated to maintain ETCO$_2$ between 35 ± 5 mm Hg. Anesthesia was maintained using α-chloralose-urethane (100 mg/kg, IV bolus followed by 10 mg/kg/hr infusion). A femoral arterial line was placed and a Swan-Ganz 7 Fr thermodilution catheter was inserted into the pulmonary artery via an external jugular vein to measure central venous (CVP), pulmonary artery (PA), and pulmonary artery wedge (PAW) pressures and cardiac output (CO). All drugs were dissolved in sterile water and normal saline was infused at approximately 5 ml/kg/hr during the study. Lead II EKG was recorded. A heating blanket was used to maintain normothermia. Serum [Na$^+$], [K$^+$], [Ca] (ionized and total) and OSM were measured. After a stabilization period of one hour, duplicate baseline measurements were obtained every 15 min. The dogs were then randomly divided into four groups with five animals in each group. Group 1 received neither dandrolene nor verapamil (control). Group 2 received three successive IV doses of dantrolene (1 mg/kg, 3 mg/kg, 6 mg/kg) at 30 minute intervals. Group 3 received verapamil 0.1 mg/kg, IV, followed by a continuous infusion of 5 μg/kg/hr. Group 4 received verapamil as in group 3; followed by dantrolene as in group 2. Measurements were obtained at 15 minute intervals for two and a half hours. Group differences were determined by one way analysis of variance and statistical significance was taken at $P < 0.05$.

Results. A progressive rise in serum [K$^+$] occurred in groups 2 and 4, being significant after 120 min. Serum total Ca in group 4 and serum Na$^+$ levels in groups 2 and 4 were significantly lower (but within normal range) than the other groups after the third dose of IV dantrolene. By contrast, there were no differences in serum ionized Ca concentrations. There were no statistically significant differences in mean arterial pressure, heart rate, PA, pulmonary vascular resistance, systemic vascular resistance or CO between groups. There were no physiological differences in arterial pH, PaCO$_2$, PaO$_2$ or serum OSM between groups throughout the study. One dog in group 4 developed a junctional rhythm after receiving the final dose of dantrolene. Otherwise, PR and QT intervals and QRS durations were similar in all groups.

Discussion. Dantrolene given alone or during verapamil infusion did not cause hemodynamic changes in our dog model. Larger doses of verapamil are perhaps required to produce cardiovascular depression in the dog.[1] Changes in serum [Na$^+$], [Ca^{++}], and OSM were physiologically insignificant and a decrease in serum total [Ca] was noted only in the verapamil-dantrolene combination group. However, dantrolene and verapamil-dantrolene both produced hyperkalemia in our dog model. These results suggest that hyperkalemia in response to verapamil and dantrolene is not specific to the pig and they should not be given together as a theoretically superior drug combination for the treatment of malignant hyperthermia.



Serum [K+] and Total Ca Levels

Each point represents the mean of 5 animals. Verapamil infusion was initiated at time 15 min while dantrolene doses were given at times 45, 75 and 105 min.

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Title: RELATIVE CARDIORESPIRATORY POTENCY OF THE ANALEPTIC TRH UNDER FOUR ANESTHETICS AND IN AWAKE RATS

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Introduction. Thyrotropin releasing hormone (TRH) is a neuropeptide possessing many interesting qualities. Its well-described analeptic actions in pharmacologic doses are of obvious relevance to anesthesiology. However, its puzzling interactive effect with other drugs in exacerbating their lethality, despite its own high safety margin, has prevented its ready application. Beyond the pharmacologic development of its practical uses, TRH is of theoretical interest in cardiovascular physiology, since 1) it is one of the most potent centrally-effective cardiovascular stimulants known, suggesting neurotransmitter or co-modulator activity, 2) it is one of the few agents known to simultaneously raise mean blood pressure (MBP) and heart rate (HR) when given centrally or peripherally, and 3) its cardiovascular actions are apparently not entirely dependent on sympathicoadrenal pathways. Although many studies have explored the ability of TRH to reverse central nervous depression induced by various anesthetics, little is known regarding the concomitant cardiovascular, respiratory, and metabolic responses to analeptic doses of TRH when given under various anesthetics and, particularly, how these responses compare to effects in the conscious (CON) state. To this end the present study was performed using a conscious rat model as a standard for comparison of the interaction of TRH with enflurane (ENF), isoflurane (ISO), ketamine (KET), and pentobarbital (PEN) with respect to central hemodynamics, respiratory rate (RR), blood gases, glucose (GLU), and lactate (LAC). The minimum alveolar concentration (MAC) of the inhaled agents was chosen as a meaningful basis for equating anesthetic dosages; amounts of the intravenous (IV) agents giving a similar depth of anesthesia under the conditions of this study were determined in pilot experiments.

Methods. Fifty-four male Sprague-Dawley rats (285 ± 4g, mean ± SEM) were divided into 5 groups, CON (N = 11), ENF (N = 12), ISO (N = 10), KET (N = 11), and PEN (N = 10). The anesthetic assigned to each group was its sole anesthetic for induction, intubation, surgery, and maintenance. Anesthetic protocols during the experimental period were: 2% ENF or 1.4% ISO in oxygen with spontaneous respiration; 60 mg/kg/hr KET (25 mg/ml) or 8 mg/kg/hr PEN (3.3 mg/ml) by continuous IV infusion with oxygen breathed spontaneously. In the CON group ENF was used for surgery, and their measurements were begun 1 hr after extubation. MBP, HR, central venous pressure, cardiac output (thermodilution), and RR measurements were made over a 20 min baseline period and for 1 hr after a 2 mg/kg IV bolus of TRH. Arterial blood samples (0.3 ml) were collected pre-TRH and at 5 min and 1 hr after TRH for determination of pH, PCO_2, PO_2, hematocrit, GLU, and LAC. The data were analyzed using repeated measures analysis of variance with a 5% significance level.

Results. The main cardiovascular and respiratory data are summarized in the table as the mean differences in the responses noted at 5 min after TRH minus the baseline values pre-TRH (listed in parentheses). With few exceptions the peak effect of TRH occurred in each parameter by 5 min and returned to baseline by 60 min or before. TRH produced a rapid increase in HR, MBP, and RR in all groups (except for MBP in PEN). The stimulant action of TRH was very pronounced in RR and persisted for at least 30 min in those groups (ENF, ISO, and PEN) where RR was depressed pre-TRH, but not with KET where RR was the same as CON pre-TRH. The large increases in RR with TRH for ISO and ENF were associated with significant decreases in arterial PCO_2 and increases in plasma LAC. TRH increased plasma GLU in all groups except ENF where baseline GLU was already markedly elevated above CON pre-TRH.

Table. Change (Post-Pre) within 5 min of TRH (2 mg/kg IV bolus) in parameters related to cardiovascular and respiratory function.

Cardiovascular Parameters (mean difference ± SEM)			
Group	HR (BPM)	MBP (mmHg)	GLU (mg/dl)
CON	30±9* (383)	7±3* (119)	33±7* (119)
ENF	33±5* (304)[a]	14±2* (82)[a]	-2±6 (162)[a]
ISO	36±12* (365)[a]	16±4* (105)[a]	45±7* (143)[a]
KET	25±6* (312)[a]	11±2* (110)[a]	11±3* (101)[a]
PEN	28±7* (408)[a]	4±4 (136)[a]	35±9* (107)

Respiratory Parameters (mean difference ± SEM)			
Group	RR (BPM)	PCO_2 (mmHg)	LAC (mg/dl)
CON	26±9* (99)	-2±1 (34)	7±1* (10)
ENF	50±5* (64)[a]	-19±2* (60)[a]	4±1* (13)[a]
ISO	64±6* (72)[a]	-5±1* (37)	14±3* (19)[a]
KET	14±5* (99)	-1±1 (40)[a]	.6±.3 (8)
PEN	21±5* (72)[a]	-6±2* (48)[a]	.4±.6 (8)

*$p<.05$ significant change from baseline (values in parentheses).

[a] $p<.05$ anesthetic baseline significantly different from CON baseline.

Discussion. The rapid increases in HR and MBP and GLU following IV TRH are suggestive of potent adrenergic actions of this neuropeptide, as noted by others. Strong primary effects of the drug are indicated by the dual action of TRH in reversing the depressant effects of the anesthetics on both the cardiovascular and respiratory systems. The cardiovascular responses to TRH were surprisingly uniform despite significant anesthetic-induced deviations from the CON baseline. This points to a peripheral site of action for TRH close to the cardiovascular and/or adrenal neuroeffector junctions, since the 4 anesthetics have varied influences on reflexogenic and central nervous circulatory control function. On the other hand, some support for an inverse relationship between the magnitude of response to TRH and the degree of anesthetic-induced depression of function can be seen in the respiratory data, indicating a predominantly central nervous effect of TRH on ventilatory control. Finally, the blood gas and lactate data confirm that in the presence of anesthetic depression of respiration TRH can produce a significant increase in alveolar ventilation, not just a volume-compensated rate increase.

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TITLE: A COMPARISON OF THE ICP EFFECTS OF ISOFLURANE AND HALOTHANE AFTER CRYOGENIC BRAIN INJURY IN RABBITS

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INTRODUCTION: The effects of halothane(H) and isoflurane(I) on cerebral blood flow(CBF) in normal animals during normocapnia have been well studied, i.e. 1 MAC H increases CBF while 1 MAC I has little or no effect(1,2). This suggests that I might offer advantages over H in the anesthetic management of patients with elevated ICP. However,no direct comparison of the ICP effects of H and I in the presence of brain injury has been performed. Thus,this study directly compared the ICP effects of H and I in animals with elevated ICP produced by a traumatic brain injury(freeze lesion).

METHODS: 20 rabbits were anesthetized with 4% H in O_2. After intubation, H was discontinued and morphine sulfate(MS) 10 mg/kg , pancuronium(P) 1 mg and 3% Evans Blue(EB) dye 3 ml were given IV. This was followed by an infusion of 2 mg/kg/hr MS and 0.5 mg/kg P. Animals were ventilated with 70% N_2O in O_2 with CO_2 added to maintain normocapnia at all times. After 0.25% bupivicaine infiltration, an arterial line was placed in the groin and the skull exposed by reflecting the tissues laterally after a midline incision. Monitored parameters were mean arterial pressure(MAP), arterial blood gases(ABGs), fronto-occipital electroencephalogram(EEG), end tidal (ET) CO_2 , ET H or I and supratentorial ICP measured with a stereotactically placed needle in the right cerebral ventricle. Following placement of the ventriculostomy needle, a funnel was fixed to the intact skull overlying the left parietal area with epoxy and animals were left undisturbed until the ET H concentration was < 0.08%. A cryogenic injury was then produced by filling the funnel with liquid N_2 for exactly 1 minute. 1 hour after lesioning, when ICP had not changed more than 1 mm Hg in the preceding 5 minutes, animals were given either H(n=10) or I(n=10). H or I was introduced over 10 minutes to achieve a 1 MAC ET concentration and was continued at that level for 15 minutes. MAP was supported at pre-volatile agent levels with angiotensin II. ICP was recorded continuously with notation made of the mean value pre-lesion, immediately before H or I administration, and at the point at which the highest mean ICP was achieved during the 15 minute period of 1 MAC administration of H or I. Animals were then sacrificed and the brains removed and placed in formalin. Changes in ICP coincident with the administration of H or I were compared within groups using a paired t-test corrected for multiple comparisons and differences between groups with a t-test for unpaired data. P < 0.05 was considered significant. Brains were inspected grossly to determine the degree of penetration of EB dye and the EEG records examined to document the presence or absence of seizure activity during H or I administration.

RESULTS: MAP and ABGs were equivalent in the two groups before the freeze lesion and at the time of H or I administration. In both groups, the lesion resulted in a significant elevation in ICP from baseline. Administration of H or I was associated with significant further increases in ICP within groups, but no intergroup differences were observed(Table 1). The ranges of ICP elevation following the lesion were roughly comparable in the two groups. Figure 1 summarizes the ICP responses to either H or I for the individual rabbits. Seizure activity was noted frequently following the insult, but was not observed during administration of either H or I. Brain damage as assessed by EB dye penetration was confined to a well circumscribed circular area centered on the left parietal cortex. No gross differences were observed between groups.

DISCUSSION: These data demonstrate that following traumatic brain injury ,in the presence of elevated ICP and normocapnia, addition of 1 MAC I is associated with ICP increases equivalent to those seen with the administration of 1 MAC H if MAP is maintained. Thus, despite the minimal increase in CBF caused by I in normal animals, significant elevation of ICP may occur when I is administered in the presence of cerebral injury. If this model is relevant to human anesthesia, these data imply that I may not confer any advatage over H with regard to the anesthetic management of intracranial hypertension when normocapnia is maintained. Studies are presently underway to determine if hypocapnia can modify the ICP responses observed in this study.

TABLE 1-MEAN ICP CHANGES

	Pre-lesion	Before H or I	Highest ICP
H(n=10)	4.6+1.6	*21.4+11.5	*30.2+12.9
I(n=10)	5.4+1.5	*19.5+10	*29.5+14.6

* Denotes significant increase from previous value within group(p<0.05, paired t-test). No significant intergroup differences were observed.

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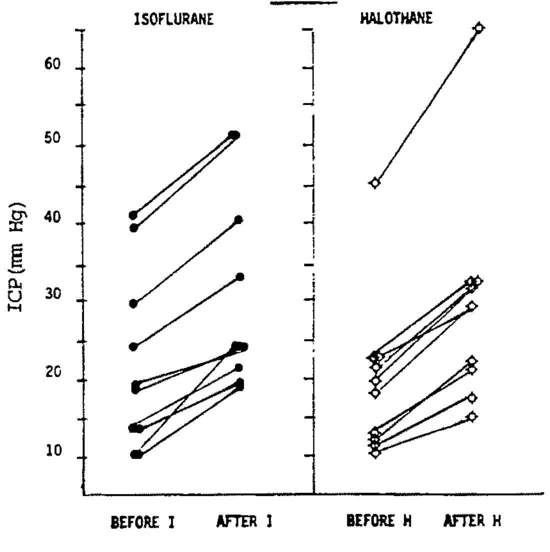
FIGURE 1



TITLE: THE EFFECT OF ACUTE HYPOCAPNIA ON HUMAN MEDIAN NERVE SOMATOSENSORY EVOKED RESPONSES

AUTHORS: A. Schubert, M.D. and J.C. Drummond, M.D. (Parker B. Francis Investigator in Anesthesiology)
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INTRODUCTION: It has been suggested that changes in arterial carbon dioxide tension (P_aCO_2) affect sensory evoked potential waveforms(1). Accordingly, it has been recommended that P_aCO_2 be kept constant during critical monitoring periods. We undertook the following study to determine the nature and magnitude of the effects of acute hypocapnia on median nerve somatosensory evoked potentials (MnSSEPs).

METHODS: Institutional approval and informed consent were obtained. We investigated 10 neurologically normal adults, aged 22-62 years, who were scheduled for elective non-neurologic surgery. After premedication (morphine 0.2mg/kg im 60 min preinduction), anesthesia was induced with sodium thiopental 4-8mg/kg, fentanyl 10-15µg/kg and relaxant. The trachea was intubated and the lungs were mechanically ventilated. Anesthesia was maintained with N_2O (65% inspired) and isoflurane (0.5% inspired). End tidal CO_2 ($ETCO_2$) was monitored with an Expanded Performance CO_2 Monitor (Puritan Bennett). Replicated unilateral MnSSEPs were obtained from surface electrodes at Erb's point, the second vertebral process (C_{II}) and the contralateral sensory cortex (C_3' or C_4'). MnSSEPs were recorded after $ETCO_2$ had been stable for 15 min at normocapnia (N) ($ETCO_2$ =37-40 mm Hg), hypocapnia (H) ($ETCO_2$ =20-22 mm Hg) and on return to normocapnia (NR) ($ETCO_2$ =38-41 mm Hg). Hypocapnia was induced by mechanical hyperventilation. The cortical waveform of interest consisted of an initial negativity (N_1) at 19-23 ms, followed by a positivity (P_1) at 22-27 ms. For each recording, mean systemic blood pressure (MAP), heart rate (HR) and esophageal temperature (ET) were noted. MnSSEPs were not recorded until at least 20 min after induction, introduction of an inhaled anesthetic and incision. To prevent cooling of the stimulated extremity, it was wrapped and the peripheral IV cannula was placed in the opposite forearm. A heater-humidifier and fluid warmer were used to maintain body temperature.

RESULTS: MAP, HR and ET were not different at H, N or NR. Spot checks of free flowing venous PCO_2 confirmed the magnitude of the step changes in $ETCO_2$. Reproducible MnSSEP waveforms were obtained in all patients. Hypocapnia resulted in a decrease in all MnSSEP latencies and had no effect on N_1-P_1 amplitude (see table). The latencies of cortical waveform components were affected to a greater extent than subcortical ones (see figure). The shortening of C_{II}, N_1 and P_1 latency achieved statistical significance at H while Erb's point latency and CCT (Central Conduction Time = C_{II}-N_1 interwave latency) did not. Although MnSSEP latencies did not appear to return completely to their pre-hypocapnia levels, there were no statistically significant differences between values observed at N and NR.

DISCUSSION: Our data indicate that acute hypocapnia produced by mechanical hyperventilation shortens MnSSEP latencies. While statistically significant, the cortical latency changes caused by a 20 mm Hg decrease in $ETCO_2$ were small and CCT remained unchanged. We therefore conclude that acute hypocapnia of a degree frequently encountered during clinical SSEP monitoring will not interfere with the accurate interpretation of MnSSEPs.

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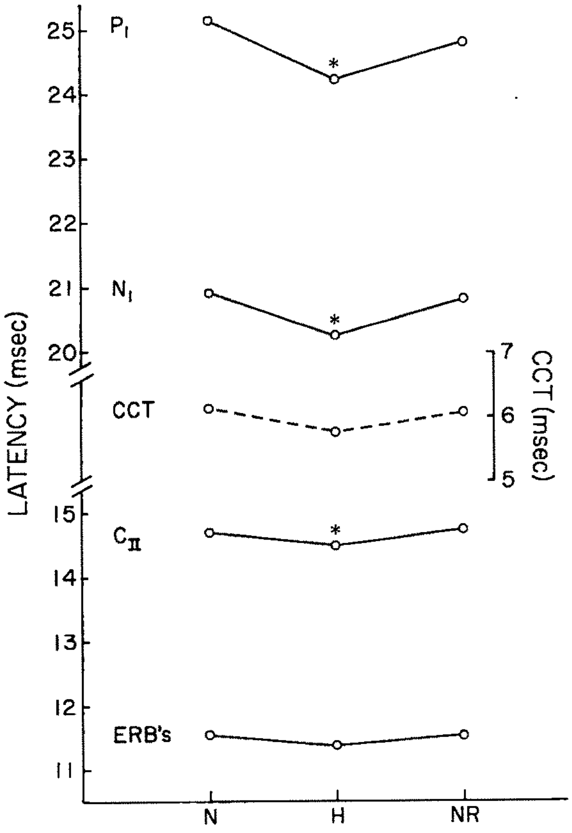
Table: MnSSEP Latency (ms) and Amplitude (µV) During Normocapnia and Hypocapnia (Mean(+-S.D.):

	N	H	NR
Erb's	11.55±0.72	11.38±0.71	11.53±0.90
C_{II}	14.80±1.14	14.50±1.13*	14.75±1.08
CCT	6.14±0.81	5.75±0.61	6.07±0.64
N_1	20.93±1.50	20.25±1.49*	20.83±1.44
P_1	25.17±2.88	24.23±2.52*	24.82±3.04
N_1-P_1 Amp	0.89±0.42	0.87±0.36	0.73±0.42

* p<0.02 vs. N or NR

Figure: Effect of Hypocapnia on MnSSEP latency (*p<0.02 vs. N or NR)



TITLE: A COMPARISON OF CO_2 AND BOLUS SALINE INJECTION AS TESTS OF ADEQUATE DOPPLER PLACEMENT IN NEUROSURGERY

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INTRODUCTION: To be useful in the detection of intraoperative venous air embolism, a precordial Doppler probe must be correctly positioned over right heart structures. Several techniques for verifying accurate probe position are in use. These include observation of the Doppler response to the injection of carbon dioxide (CO_2) or a small fluid bolus through either a central or a peripheral venous catheter.[1] However, the validity of the fluid bolus method has been questioned because the mechanical disturbance caused by a bolus of fluid rapidly injected into the central circulation may be transmitted across the intracardiac septum. This could result in false verification of the placement of a Doppler probe which is actually monitoring only left heart structures, with subsequent inability to detect intraoperative venous air embolization. To clarify this issue, we have examined the responses of a conventionally placed parasternal probe to both peripheral and central injection of normal saline (NS) and (CO_2), and compared these with the responses from a probe intentionally malpositioned laterally over the left precordium.

METHODS: With institutional approval and informed consent, we studied 18 consecutive adults (ages 18-74) undergoing elective craniotomy. After induction of anesthesia and tracheal intubation, the lungs were mechanically ventilated at tidal volumes of 10 ml/kg. A multiorificed central venous catheter (Bunegin-Albin Air Aspiration Set, Cook Inc.) was inserted via the antecubital route, with the tip positioned at the SVC-atrial junction[2,3]. Doppler sounds were monitored with two P-81 ultrasound probes attached to separate Versatone (MedSonics Inc.) units. Probe (R) was placed at the conventional location along the right parasternal border between the 3rd and 6th intercostal spaces. If a good signal could not be elicited at this location (3 patients), the left parasternal location yielding the best signal was selected. Probe (L) was positioned as far laterally on the left precordium as was consistent with a Doppler signal of good quality. Both probes were secured with adhesive tape. The patients then received a systematially varied sequence of 4 IV injections of room temperature NS (10 ml) and CO2 (1 ml) given via the central and peripheral (16g, forearm) venous catheters. Injections were made as rapidly as possible through a stopcock 50 cm proximal to the hub of the central or peripheral IV catheter, through which a crystalloid infusion was maintained at 200-300 ml/hr. After each injection, Doppler sounds were allowed to return to normal with a minimum of 3 min elapsing between injections. All injections were completed prior to headholder placement and skin incision and were performed with patients in the semi-recumbent position. Simultaneous audiotape recordings of the output of each Versatone were made. The tapes were later analyzed and Doppler responses to the test injections graded by blinded observers as either positive or negative.

RESULTS: Technically satisfactory recordings were obtained in 17/18 patients. Results are summarized in the table. NS injected via the central catheter elicited a positive response from R in all patients (17/17), but also yielded a positive response at L in 13/17 patients. By contrast, CO_2 injected via the central catheter was detected by 15/17 R probes, as compared with only 5/17 L probes. The difference in the response rates at the L probe was significant ($p < .015$). The positive response rates to peripheral NS and CO_2 are included in the table for comparison. However, the subsequent discussion will principally address the response to injections via the centrally placed catheter.

DISCUSSION: These data indicate that the use of centrally injected NS as a means for testing Doppler probe positioning can yield false positive verification of accurate placement. The observation that the laterally placed probe L yielded a positive response to CO_2 in some patients suggests that its field of detection occasionally included right heart structures. This, in turn, suggests that relatively leftward probe placement may, on occasion, provide satisfactory air detection. However, while the L probe detected gas after 29% of central CO2 injections, the positive response rate for central NS at L was 76%. The difference (47%) indicates that bolus NS injection can yield a positive response where gas bubbles will not. One explanation for this may be that NS, forcefully injected through a centrally placed catheter, produces sufficient turbulence and/or vibration to cause movement of left heart structures of a magnitude detectable by the malpositioned Doppler probe.

We conclude that under the conditions of the present study, when Doppler probe placement is tested by means of a centrally injected NS bolus, false positive confirmation of adequate doppler probe placement can occur. This could result in the subsequent failure to detect intraoperative air emboli in some patients. This may be particularly relevant when right parasternal placement is not attainable and alternate locations for probe placement must be utilized.

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Table: Number of Positive Responses (%) to Central and Peripheral NS and CO2 (n=17).

	CENTRAL		PERIPHERAL	
	NS	CO_2	NS	CO_2
R	17 (100%)	15 (88%)	14 (82%)	11 (65%)
L	13 (76%)	5 (29%)*	5 (29%)	3 (18%)

* p<0.015 vs. NS; other central and peripheral CO2/NS comparisons ns (Fisher's exact test). Nevertheless, the positive response rate at L for central NS (76%) was significantly in excess of that observed with central CO_2 injection (29%).

TITLE: THE EFFECT OF HIGH-DOSE FENTANYL ON HUMAN MEDIAN NERVE SOMATOSENSORY EVOKED RESPONSES

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INTRODUCTION: Although the effect of low dose IV fentanyl on human somatosensory evoked potentials (SSEPs) has been reported previously[1,2], high doses have not been studied systematically. Yet, high dose fentanyl is often an appropriate anesthetic technique for patients who require intraoperative SSEP monitoring. We investigated the effect of high dose fentanyl on median nerve SSEPs in patients undergoing cardiac surgery.

METHOD: Having obtained institutional approval and informed consent, we studied nine neurologically normal adult patients, aged 45-84 years, who were scheduled for elective cardiac surgery. After premedication (diazepam 0.1-0.2mg/kg po, morphine 0.08-0.15mg/kg im 60-90 min preinduction), unilateral median nerve SSEPs were obtained from surface electrodes at Erbs's point, the 2nd cervical vertebral process (C_{II}) and the contralateral sensory cortex (C_3' or C_4'). The cortical waveform of interest consisted of an initial negativity (N_1) at 20-24 ms, followed by a positivity (P_1) at 22-27 ms. Mean systemic arterial pressure (MAP), core temperature (CT) and arterial blood gas tensions (ABG) were measured. Anesthesia was then induced with O_2, relaxant and fentanyl. Fentanyl was administered as a slow IV bolus (mean dose 53µg/kg; range 36-71µg/kg) over a period of 10-20 min, followed by an infusion of 10-20µg/kg/hr. Ventilation was adjusted to maintain a normal end tidal CO_2 ($ETCO_2$). SSEP recordings were repeated 20 min (t=20) and 45 min (t=45) after induction of anesthesia. MAP, CT and ABGs were noted. To prevent local cooling, the stimulated extremity was wrapped and the peripheral IV cannula was placed in the opposite arm. A heater-humidifier, fluid warmer and heating blanket were employed to maintain CT.

RESULTS: MAP was unchanged from control at t=20 and t=45. CT was 36.02 ± 0.47°C preinduction, 35.57 ± 0.70°C at t=20 (n.s.) and 35.37 ± 0.61°C at t=45 (p<0.05 vs. control). Pre- and postinduction ABG's confirmed adequate oxygenation. Although reproducible preinduction SSEP waveforms were obtained in all nine patients, noise artifact prevented identification of the Erbs's point potential in two patients. Cumulative fentanyl doses of 55.0±8.6 µg/kg at t=20 and 63.6±10.1 µg/kg at t=45 resulted in an increase in all SSEP latencies and a decrease in the N_1-P_1 amplitude (see table). The cortical components of the SSEP were affected to a greater extent than subcortical ones. Amplitude and latency values at t=20 were not statistically different from those obtained at t=45 (see figure).

DISCUSSION: Despite small but statistically significant changes in latency and amplitude, the SSEP waveforms remained consistently recordable and interpretable. We conclude that median nerve SSEPs can be effectively monitored during high dose fentanyl anesthesia. However, accurate interpretation, particularly of cortical waveform changes, must take into account the magnitude and time course of fentanyl's effect on the evoked response.

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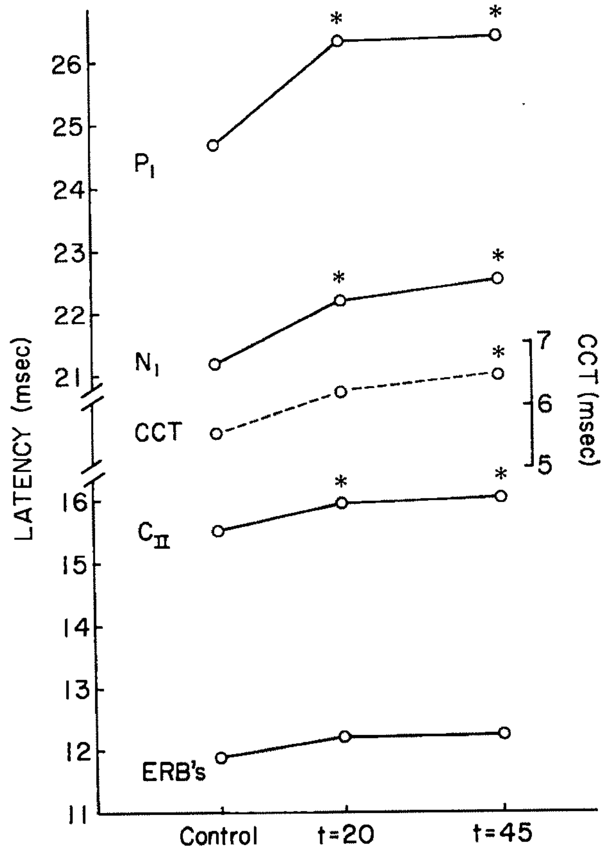
Table: Latency (ms) and Amplitude (µV) Prior to and During High Dose Fentanyl (Mean ± S.D.) (n=9#).

	Control	t=20 min	t=45 min
ERB's	11.89±1.18	12.21±1.69	12.22±1.70
C_{II}	15.52±1.65	15.96±1.52*	16.02±1.54*
CCT	5.59±0.94	6.23±0.99	6.48±1.18*
N_1	21.18±1.42	22.18±1.55*	22.50±1.52*
P_1	24.68±2.81	26.32±2.46*	26.36±2.50*
N_1-P_1 Amp	2.04±1.30	1.31±0.74*	1.33±0.74*

CCT (Central Conduction Time)=C_{II}-N_1 interwave latency. * p<0.02 vs. control; # n=7 for Erb's.

Figure: Effect of High Dose Fentanyl on SSEP latencies at t=20 and t=45 (* p<0.02 vs. control).



Title: THE CLINICAL PHARMACOLOGY OF HIGH DOSE ATRACURIUM

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Introduction: Atracurium has a moderately fast onset at the high end of the recommended clinical dose range (0.5 mg/kg).[1] Recently it has been suggested that 0.8 mg/kg may provide satisfactory intubating conditions at 90 seconds without significant haemodynamic changes.[2] Other studies, however, have shown that at 0.6 mg/kg there is a significant reduction in mean arterial pressure in association with histamine release.[1] This study was designed to determine the safety and efficacy of administering 0.8 mg/kg of atracurium to healthy patients. The clinical pharmacology, in particular the speed of onset and the haemodynamic response to a variety of administration techniques, was studied. Some of this data is compared to data obtained previously under the same protocol but at a lower dose level (0.5 mg/kg).

Methods: Fifty-six (ASA Class 1 or 2) patients gave institutionally approved informed consent to the study and were assigned to one of seven subgroups. Premedication consisted of 0.1 mg/kg morphine I.M. and 0.2 mg/kg diazepam orally. In groups 1 to 5 anaesthesia was induced with fentanyl 5 μg/kg and pentothal 5 mg/kg and ventilation was controlled with nitrous oxide and oxygen (4L:2L). Heart rate (by tachograph), EKG, intra-arterial blood pressure, and single twitch adductor response at the thumb were continuously recorded. After a stable baseline period, 0.8 mg/kg atracurium was administered over 5 sec to patients in groups 1 and 5; over 30 sec to patients in group 2; and over 75 seconds to patients in group 3. Patients in group 4 received a priming dose of 0.08 mg/kg followed 6 minutes later by a bolus dose of 0.72 mg/kg. Patients in group 5 were pretreated with cimetidine 4 mg/kg IV and chlorpheniramine 0.1 mg/kg IV 15 minutes before induction. Maximum changes in mean arterial pressure and heart rate were recorded. Plasma samples for histamine levels were drawn before injection of atracurium and at 2 and 5 minutes after injection. In groups 6 and 7, anaesthesia was induced with pentothal 5 mg/kg only. Group 6 patients received a priming dose of atracurium 0.08 mg/kg 5.5 minutes prior to induction followed by a bolus of 0.72 mg/kg 30 sec after induction. Patients in group 7 received a bolus of 0.8 mg/kg atracurium 30 seconds after induction. Patients in these two groups were intubated 90 seconds following this large dose of atracurium and intubating conditions were classified as excellent, satisfactory, fair or poor (grades 1-4) according to the criteria of Lund and Stovner.[3]

Results: Cardiovascular effects (see Table 1). Patients in groups 1, 2, and 4 demonstrated a transient but significant reduction in mean arterial pressure following administration of atracurium. Pharmacodynamics (see Table 2).

Data obtained previously under the same protocol but at a lower dose level (0.5 mg/kg) are displayed in brackets.

Conclusion: 0.8 mg/kg atracurium produces a faster onset time than 0.5 mg/kg ($p < 0.05$). The intubating conditions are good to excellent at 90 seconds and the intubation score is the same as that produced by 0.5 mg/kg at 150 seconds. Priming produces no significant improvement in onset times or intubating conditions at this dose. However, onset times under nitrous narcotic anaesthesia are significantly faster than under pentothal alone ($p < 0.05$).

The transient reduction in mean arterial pressure and the significant rise in histamine levels ($p < 0.01$) observed following a 5 second bolus can be attenuated by slowing the administration of atracurium to 75 seconds. Antihistamine pretreatment only offers partial haemodynamic protection whereas priming or a 30 second injection offers no protection at this dose level.

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TABLE 1 CARDIOVASCULAR DATA
Mean Values (SE's omitted for space)
Maximum change expressed as a % of control

	MAP	HR	Histamine
Group 1 5 sec bolus	74.6**	113.2	295
Group 2 30 sec bolus	77**	114.7	471
Group 3 75 sec bolus	95.7	102.6	118
Group 4 Prime	76**	109.3	923
Group 5 H_1 & H_2 blockers	83.3*	109.9	1268

MAP = Mean Arterial Pressure
HR = Heart Rate
t-test
* $0.05 < p < 0.1$
** $p < 0.05$

TABLE 2 PHARMACODYNAMIC DATA
Mean Values (SE's omitted for space)

	Onset. (mins) End injection to Complete block	Recovery. (mins) 5-95%	Duration. (mins) Injection to 95% Recovery
Group 1 5 sec bolus	1.82 (2.3)	20.8 (24)	70 (59)
Group 3 75 sec dose	1.71	24	69.7
Group 4 Prime	1.9	29.8	81.25
Group 5 H_1 & H_2 prophylaxis	2.0	30.75	83.1
Group 6 Prime (pentothal only)	3.0		
Group 7 5 sec bolus (pentothal only)	3.48 (4.6)		

All data in brackets refers to 0.5 mg/kg Atracurium (n=10)

Title: PHARMACOKINETICS AND PHARMACODYNAMICS OF METOCURINE IN CARDIAC SURGERY PATIENTS

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Introduction. The cardiovascular stability associated with metocurine (MTC) administration makes it suitable for use with patients at risk from myocardial ischemia. This study examines the kinetics of MTC in patients scheduled for coronary artery bypass surgery, and assesses the adequacy of neuromuscular blockade when MTC is administered according to a predetermined bolus and infusion regimen intended to maintain a plasma MTC concentration of 0.63 ug/ml.

Method. The 10 male patients who gave written informed consent to this institutionally-approved study did not have symptomatic or biochemical evidence of renal or hepatic disease. All were receiving beta-adrenergic receptor-blocking drugs and nitrates. Following premedication with intramuscular morphine, 6-12 mg, anesthesia was induced with fentanyl, 0.15 to 0.5 µg, and was maintained with halothane, 0.5-1.5% in oxygen. Once anesthesia was deemed adequate, the ulnar nerve was stimulated supramaximally with four stimuli of 0.2 msec duration at 2Hz every 20 sec. Control values of the rectified integrated electromyogram (EMG) were obtained prior to MTC administration. Paralysis was calculated as depression of the first response compared with its control value. The dosage regimen for metocurine was a bolus of 0.3 mg/kg, given concurrently with the commencement of MTC infusion at .04 mg/kg/hr. Plasma samples from arterial blood were obtained at -5, 2, 5, 10, 15, 20, 30, 45 and 60 min, and then at half-hour intervals during the infusion: the first 2 hours of the sampling schedule were recommenced in the post infusion period, continuing at 2, 4, 6, 8, and 12 hr. Additional samples were taken immediately before commencement of cardiopulmonary bypass (CPB), and at 2, 5 and 10 min after. Aliquots of plasma and urine were stored at -40C for later determination of metocurine concentrations, [MTC], by an HPLC technique.[1] Intraoperative temperatures were measured by a thermistor placed in the nasopharynx.

Results. The pharmacokinetics of metocurine resembled those in a group of patients undergoing hip surgery (table 1).

Table 1: Pharmacokinetics of metocurine, mean (SD)

	CPB group	Control
Volume of distribution, V_{SS}. 1/kg	0.34(0.05)	0.35(0.0)
Clearance ml/kg/min	1.1(0.2)	1.2(0.2)
Elimination half life, h	4.4(0.9)	4.0(0.8)

A plot of the metocurine plasma concentration time data for all patients, showed a tendency to plateau during the first hour of the infusion. This curve was interrupted by the dilutional effect of initiating cardiopulmonary bypass (CPB). This period of reduced plasma concentrations seldom lasted more than 10 min and there was a plateau in metocurine plasma concentrations thereafter. The intensity of neuromuscular blockade lessened with the start of CPB, and decreased further to stabilize at 73(18)% paralysis during hypothermia. With rewarming, the plasma concentrations of MTC were unchanged, but neuromuscular blockade intensified, to return to values observed before CPB. (table 2)

Table 2: Hypothermic CPB and metocurine

	Temperature, °C	Paralysis %	[MTC] µg/ml
Before CPB	36.1(0.4)	88(11)	.79(.12)
CPB + 10 min	32.3(2.4)	78(20)	.62(.05)
CPB + 45 min	29.8(0.4)	72(16)	.65(.08)
Rewarming	30.2(0.5)	73(18)	.67(.06)
CPB ends	36.6(0.6)	86(8)	.67(.05)
Infusion ends	36.5(0.5)	87(8)	.67(.05)

Discussion. The pharmacokinetics of MTC were affected minimally by hypothermic CPB. This differs from studies involving bolus and infusion studies of alcuronium[2] and tubocurarine,[3] in which the apparent volume of distribution was unchanged, but the elimination half-life was prolonged and the plasma clearance markedly reduced. The changes in neuromuscular blockade with the onset of CPB could have been due to both dilution of its concentration in the body fluids and to cooling at the sites of neuromuscular transmission. The return to the original intensities of blockade with rewarming confirms that there is a decreased sensitivity to the effect of MTC at lower temperatures.

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Title: REBOUND PULMONARY ARTERY HYPERTENSION FOLLOWING SODIUM NITROPRUSSIDE INDUCED HYPOTENSION

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Introduction: Rebound arterial and pulmonary hypertension has been reported to occur following discontinuation of sodium nitroprusside (SNP)-induced hypotension in animals and humans.[1,2,3] The previous works attributed the mechanism of this undesirable side effects to the persistance of endogenous vasoconstrictors released as part of the normal response to hypotension, coupled with the rapid disappearance of SNP. Khambatta[2] has shown that plasma renin activity remains elevated for some time after halting SNP. However, the elevated renin-angiotension activity does not adequately explain venous or pulmonary artery hypertension. The author hypothesized that the rebound of venous and pulmonary artery pressure may be due to the central redistribution of blood volume and therefore, related to the levels of PCWP at the time of discontinuation of SNP. This study was designed to test this hypothesis.

Methods: Twenty patients from the age of 13 to 43, who underwent spine surgery with hypotensive anesthesia were studied with insititional approval. All patients were monitored with a triple-lumen flow directed catheter. The patients were divided into two groups by the degree of hydration during surgery. In group I (n=10), pulmonary capillary wedge pressure (PCWP) were maintained at the level between 6-8 mmHg during deliberate hypotension. In group II (n=10), PCWP were maintained at the level of 9-12 mmHg by intravenous fluid therapy. There were no differences between groups in age, blood loss, and anesthetic management. Anesthesia was induced with sodium-thiopental 5 mg/kg and droperidol 0.1 mg/kg and maintained with fentanyl (15-22 µg/kg), 67% nitrous oxide in oxygen and isoflurane 0.5-1%. Hypotension was induced by SNP and mean arterial pressure was maintained at 50-60 mmHg with the adjustment of SNP dose between 2-8 µg/kg·min. Blood loss were replaced ml to ml. Hemodynamic measurements were performed prior to induction (P), every 30 minutes during hypotension (H) 15 and 30 minutes after halting SNP infusion (DC 15, DC 30), on arrival at recovery room (RR).

Results: (1) In group 1, mean pulmonary artery pressure (MPAP) peaked at DC30. In group 2, a significant increase occurred at DC15 and remained elevated at DC30 and RR, and differences between group 1 and 2 were significant (p<0.05). (2) Maximum increases of MPAP during 30 minutes period following SNP halt were correlated with the maximum increases of PCWP, (r=0.73, $p<10^{-3}$) and CVP (r=0.71, $p<10^{-3}$) and not correlated with pulmonary vascular resistance index (PVRI) (r=0.36, p>0.05). 3) There were significant differences between the groups in MPAP, PCWP, CVP, and cardiac index (CI). (4) In group 2 patients, PCWP were higher than 18 mmHg in 7 patients out of 10 and giant V-waves were observed in 7 out of 10 patients during the 30 minutes period following the SNP halt While in the group 1 patients, PCWP exceeded 18 mmHg in 1 patient and giant V-waves were observed in only 1 patient during the recovery from hypotension. These incidences were significantly lower than in group 2 (p<0.05). (5) Increases of MPAP was not associated with the increases of the pulmonary artery diastolic pressure-PCWP differences.

Discussion: Todd[3] reported that rebound pulmonary arterial hypertension was seen in the dogs given SNP. In their report, this increase of MPAP was related to the increase of PVRI. Contrary to their findings, we found that the increase of MPAP was not related to the changes in PVRI and the increase of MPAP, CVP and PCWP were parallel following the halt of SNP. The rebounding patterns of PMAP, PCWP, and CVP resemble that of fluid overload, and appearance of giant V-waves may suggest over-filling of the left atrium. Our observations support our hypothesis that central redistribution of blood volume from venous capacitance vessels is the main contributory factor of rebound pulmonary and venous pressures.

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Table 1

		P	H	DC15	DC30	RR
HR	Gr1	89	102	79^{a}	76^{b}	106^{cd}
	Gr2	89	87^{*}	66^{ab}	71^{ab}	115^{abcd}
MAP	Gr1	87	56^{a}	102^{ab}	103^{ab}	106^{ab}
	Gr2	91	55^{a}	98^{b}	102^{b}	107^{b}
MPAP	Gr1	14	13	17^{b}	19^{ab}	18^{b}
	Gr2	16	16	20^{ab}	22^{*ab}	23^{*ab}
PCWP	Gr1	10	7	11^{b}	12^{b}	9
	Gr2	12^{*}	11^{*}	16^{*ab}	18^{*ab}	15^{*abd}
CVP	Gr1	7	6	10^{ab}	10^{ab}	8^{b}
	Gr2	9^{*}	9^{*}	13^{*ab}	14^{ab}	12^{ab}
CI	Gr1	3.7	2.9^{a}	2.7^{ab}	2.7^{a}	4.3^{*bcd}
	Gr2	3.7	3.3	2.8	2.9^{a}	5.6^{abcd}
SVRI	Gr1	1823	1426	2837^{ab}	2929^{ab}	1877^{cd}
	Gr2	1808	1154^{a}	2498^{ab}	2497^{ab}	1517^{cd}
PVRI	Gr1	110	165	188	206^{a}	179
	Gr2	103	122	134^{*}	130	119

Values are means. * p<0.05 between the groups; a, p<0.05 as compared to C; b, p<0.05 as compared to hypo; c, p<0.05 as compared to DC15; d, p<0.05 as compared to DC30. Abbreviations used are: Gr1, Group 1, Gr 2, Group 2, HR, heart rate (beats/min); MAP, mean arterial pressure (mmHg); MPAP (mmHg); PCWP (mmHg); CVP (mmHg); CI ($l/min \cdot m^2$); SVRI, systemic vascular resistance index ($dynes.sec./cm^5 \cdot m^2$); PVRI, pulmonary vascular resistance index ($dynes.sec/cm^5 \cdot m^2$).

Title: ANESTHETIC CONSIDERATIONS IN PATIENTS RECEIVING RITODRINE THERAPY FOR PRETERM LABOR

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Introduction. Preterm labor and delivery constitute major problems in obstetrics. The first line tocolytic agents are often beta adrenergic agonists. Ritodrine hydrochloride is the only such drug approved for use in the United States(1). Despite appropriate use of tocolytic therapy, some preterm deliveries are unavoidable, and cesarean section is often the mode of delivery. The interactions of beta-agonist tocolytics with anesthetic agents pose potential problems for anesthetic management(2). In addition, parenteral administration of ritodrine has been associated with a number of cardiovascular complications of mothers(3). This report details the experience of the anesthetic management of cesarean section in patients who received intravenous ritodrine to arrest preterm labor.

Method. Twenty patients who had undergone a cesarean section following failure to arrest preterm labor with intravenous ritodrine therapy were reviewed and analyzed. Maternal heart rate, blood pressure and serum potassium level before ritodrine infusion, during ritodrine infusion, upon discontinuation of the infusion, and on induction of anesthesia were reviewed and analyzed as an index of beta adrenergic activity of the drug. Cardiovascular complications of mothers in epidural and general anesthesia groups were compared with regard to the time elapsed from the discontinuation of ritodrine infusion to induction of anesthesia. Epidural anesthesia was performed using 0.5% bupivacaine, and general anesthesia consisted of thiopenthal induction, endotracheal intubation with succinylcholine and maintenance with oxygen-enflurane(0.75-1.0%) until delivery of infant.

Results. The eleven patients given epidural anesthesia and nine patients given general anesthesia were comparable in age, gestational age and infusion rate of ritodrine. Mean maternal heart rate on discontinuation of the drug was 128±12 bpm, and it took 30 to 60 minutes to show a significant decrease in heart rate (table 1). Serum potassium level showed a moderate decrease during ritodrine infusion (from 3.7 to 3.2 mEq/L) and returned to preinfusion level in 30 to 60 minutes after discontinuation of the drug infusion. One ventricular arrhythmia and three hypotensive episodes were observed in the epidural anesthesia group. No anesthetic complications were noted in the general anesthesia group. 2 out of 3 maternal hypotensive episodes under epidural anesthesia developed in patients induced within 30 minutes following the discontinuation of ritodrine infusion(table 2).

Conclusion. Significant residual betamimetic effects of ritodrine, maternal tachycardia and hypokalemia, persisted longer than 30 minutes after discontinuation of the drug, and the incidence of maternal hypotension under epidural anesthesia was higher in patients induced within 30 minutes following discontinuation of the drug. Based on our findings, we recommend that anesthesia be deferred at least 30 minutes following discontinuation of ritodrine in order to minimize the drug interactions with anesthetics and subsequent complications provided that such a delay does not jeopardize the fetus.

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Table 1. Maternal heart rate and blood pressure changes after ritodrine infusion

	Heart Rate (bpm)	Systolic Pressure (mmHg)	Diastolic Pressure (mmHg)
Before Ritodrine	95±8	121±16	74±13
On Discont. Ritodrine	128±12^a	110±21	49±13^a
30 min. After discont.	122±5^a	130±21	55±13^a
30- 60 min. After discont.	117±2^{ab}	112±19	65±13^{ab}
60 min. After discont.	104±11^b	117±14	73±12^b

^{a}p<0.01 compared with Before Ritodrine
^{b}p<0.01 compared with On discont. Ritodrine

Table 2. Time of induction after ritodrine and complications of anesthesia

Time of induction	< 30 min.		30-60 min.		> 60 min.	
Anesthesia	Epi. N=3	Gen. N=2	Epi. N=2	Gen. N=2	Epi. N=6	Gen. N=5
Hypotension	2	0	0	0	1	0
Ventricular arrhythmia	1	0	0	0	0	0

Title: EFFECT OF TEMPERATURE, BLOOD PRESSURE, AND CARDIOPULMONARY BYPASS FLOW ON EVOKED POTENTIAL LATENCY

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Introduction The intraoperative monitoring of somatosensory evoked potentials (SEP) is gaining increasing favor in surgery in which the central nervous system (CNS) is at risk of compromise(1), including neurosurgical, orthopedic, vascular, and cardiac procedures. In cardiac surgery, systemic hypothermia is often induced during cardiopulmonary bypass (CPB); hypothermia is known to be associated with a prolongation in SEP latency(2), but a similar effect may also result from reductions in cerebral perfusion. In order for SEP monitoring to fulfill a useful role as an indicator of cerebral hypoperfusion during cardiac surgery, one must be able to reliably distinguish between these events. The purpose of this study was to assess the effects of changes in body temperature, mean systemic arterial pressure (MAP) and CPB flow on SEP latency in order to determine if a reliable relationship between these variables and their effects could be established. We wished to examine the effects on both the peripheral and central nervous systems, since increases in central peak latency may in part be due to increased peripheral conduction time.

Methods With informed consent, electrodes for monitoring SEPs were placed prior to induction of anesthesia in 21 patients undergoing coronary artery bypass surgery. Stimulating electrodes, (a pair of pediatric sized ECG electrodes), were placed over the median nerve at the left wrist; sensing electrodes were placed over the ipsilateral Erb's point and over the contralateral parietal cortex; a forehead lead was used for reference and a forearm plate for ground. The median nerve was stimulated with 0.2 msec. square wave impulses at a rate of 5.7 Hz for a total of 256 repetitions; the intensity of the voltage output was adjusted to motor threshold. Evoked responses were computed and printed out on a Neurotrac^R system, prior to and following induction of anesthesia, and at regular intervals throughout the procedure, with special attention being paid to the cooling and rewarming phases, and to flow reductions while on total CPB. Fentanyl, in an induction dose of 50 to 75 mcg/kg, followed by 0.5 mcg/kg/min until the patient was rewarmed on CPB was used for anesthesia in conjunction with pancuronium and 100% oxygen. Data was analyzed by linear regression, t-tests, and analysis of variance; a p level of <0.01 was regarded as significant.

Results We performed satisfactory analysis on data from 16 patients out of the 21 studied, 5 patients being omitted because of technical problems with data collection. Separate analyses of cooling and rewarming phases showed no significant differences between them. A linear correlation was found between temperature and both peripheral and central SEP latencies. The figure depicts the means of latency to Erb's point (representing peripheral conduction), and the interval latency between Erb's point and the first cortical peak (representing central conduction). There was a much weaker correlation between MAP and SEP peak latency, both central and peripheral. Induction of anesthesia was associated with significant prolongation of the first cortical peak latency; however, there was also a significant concommitant decrease in body temperature, which might account for part of the latency prolongation. There were no significant changes in latency with the onset of CPB, with flow reductions to one half of baseline for up to 5 minutes during hypothermic CPB, or with weaning from CPB. Latencies of both central and peripheral SEP peaks returned to baseline following rewarming and termination of CPB. No patient demonstrated gross neurological deficits postoperatively.

Discussion Our data demonstrates that hypothermia increases the latency of both peripheral and central SEP peaks in a linear fashion. The diagram shows a greater slope for latency vs temperature for central conduction than peripheral, suggesting that the former is more susceptible to the effects of hypothermia than the latter. It also implies that part of the increase in latency of central peaks with hypothermia must be due to increases in peripheral conduction times. The lack of change associated with flow reductions and MAP decreases during hypothermic CPB may be due to cerebral protective effects of hypothermia although it should be noted that no corrections in pump flow for temperature decreases were made. The return of latencies to baseline upon rewarming and the lack of any gross neurological deficits postoperatively emphasizes the likelihood that the changes observed were due to temperature alterations. SEPs may potentially be a useful non-invasive monitor of the CNS during CPB, in which increases in SEP latency unaccounted for by changes in temperature may be indicative of cerebral ischemia.

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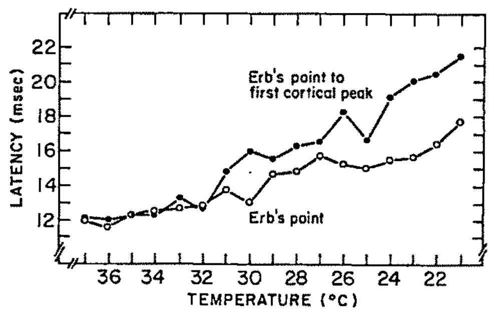

Title: PHARMACOKINETICS AND PHARMACODYNAMICS OF EDROPHONIUM IN THE ELDERLY

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Introduction. A recent review of the action of nondepolarizing muscle relaxants in the elderly pointed out that the effect of most of the relaxants is prolonged (1). Thus it is of vital importance to determine in elderly patients the distribution, elimination and actions of the drugs used to reverse the effects of muscle relaxants. In this study edrophonium was employed to reverse a steady-state neuromuscular blockade and differences between elderly and younger patients was assessed.

Methods. Five elderly patients (ages 76-87) and five younger patients (ages 27-49) scheduled to undergo elective craniotomy were studied after obtaining institutional approval and informed consent. All patients had normal renal and cardiac function and were receiving no medications known to interact with muscle relaxants. Anesthesia was induced with thiopental, and tracheal intubation was facilitated with succinylcholine (Sch). Anesthesia was maintained with $N_2O:O_2$ (60:40%) in addition to 1 MAC halothane, the inspired concentration adjusted for age. Mechanical ventilation maintained moderate hyperventilation ($PaCO_2$, 25-35 torr) and esophageal temperatures were maintained at 35.5-36.8°C. Neuromuscular transmission was assessed employing a force displacement transducer to determine twitch height of the adductor of the thumb in response to supramaximal stimulation of the ulnar nerve. Responses to single stimuli of 0.15 ms duration delivered at a frequency of 0.1 Hz were recorded. After return of twitch height to normal, a bolus of 0.1 mg/kg of metocurine was given, followed by a continuous infusion of metocurine to achieve 90% paralysis. After at least 30 min of observation, to ensure a constant twitch height, a bolus of atropine (0.02 mg/kg) was given iv followed by edrophonium (1 mg/kg), the infusion of metocurine remaining constant. Heparinized blood samples were drawn from an arterial catheter at 1, 3, 5, 10, 20, 30, 45, 60 min, and 1.5, 2, 2.5, 3, 3.5 and 4 hr. Plasma was separated and frozen until assayed by high performance liquid chromatography (HPLC), sensitivity 10 ng/ml.

Plasma concentration-time curves were fitted by using weighted least squares nonlinear regression. Pharmacokinetic parameters were determined using a method for bolus iv injection of a drug. Following injection of edrophonium, the following times of recovery from neuromuscular blockade were recorded: start of recovery, 50% recovery, maximum recovery and duration of maximal response. As response to edrophonium diminished, additional samples were drawn if any significant change in response was observed that fell between kinetic sampling times. The log plasma concentration-response curves were constructed for the linear portion of the plasma concentration-response curve between 20 and 80% paralysis for each patient and the concentration of edrophonium at 80, 50 and 20% paralysis was calculated. Comparisons between the pharmacokinetic and pharmacodynamic parameters were made by applying Student's t-test for unpaired data (two-tailed).

Results. Plasma decay curves for edrophonium in both groups are best described by a biexponential equation. The relationship for the elderly is described by the equation $C = 23.8e\text{-}^{0.6t} + 1.36e\text{-}^{0.0086t}$ and for the younger group $C = 11.5e\text{-}^{0.58t} + 0.81e^{-.014t}$ where C is µg/ml and t is min. The pharmacokinetic data are presented in Table 1. Response times for the two groups are presented in Table 2. There is no significant difference between the log plasma concentration-response data for either group.

Discussion. The data demonstrate a prolonged elimination half-life and decreased Clp of edrophonium in the elderly group. This conforms to the observation that approximately 70% of edrophonium is excreted renally (2) and that both glomerular filtration rate and tubular excretory capacity declines predictably in old age (3). Given the fact that there is no difference between the log plasma concentration-response data for both groups and the above pharmacokinetic differences, one might expect an increase in duration of response to edrophonium in the elderly. Our data do not bear this out.

Cronnelly, in a dose-response study of edrophonium has also reported that the duration of antagonism of neuromuscular blockade was not different in elderly patients compared with younger patients (4). In the same study he noted that increasing the dose of edrophonium from 0.125 to 0.5 mg/kg did not prolong the duration of antagonism in either group. In this study, employing a larger dose of edrophonium (1 mg/kg), although we found no difference in duration of antagonism between elderly and younger controls, the total duration of antagonism in min was approximately twice that reported by Cronnelly. In addition, we found no difference in onset of action between the two groups. These differences may be due to the larger dose of edrophonium employed in this study. Nonetheless, in this study and that of Cronnelly, age apparently has no effect on the duration of action of edrophonium. The explanation for this observation is not clear.

Supported in part by NIH Grant GM-26745.

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Table 1. Pharmacokinetic Parameters (Mean ± SD)

	Young, n=5 (27-49 yrs)	Elderly, n=5 (76-87 yrs)	P
$t_{1/2}$ elim (min)	53.8 ± 16	85.0 ± 19	<.025
Clp ($ml \cdot kg^{-1} \cdot min^{-1}$)	13.3 ± 5	5.1 ± 1	<.005
V_i (l/kg)	0.19 ± 0.17	0.041 ± .006	NS
Vd_{area} (l/kg)	1.07 ± 0.6	0.6 ± 0.1	NS

Table 2. Response Times (Min, Mean ± SD)

	Young, n=5 (27-49 yrs)	Elderly, n=5 (76-87 yrs)	P
Time to Maximum Response	1.6 ± 0.7	2.2 ± 0.2	NS
Duration of Maximum Response	1.2 ± 0.6	2.4 ± 1.2	NS
Time to 50% Response	113.6 ± 80	116.5 ± 46	NS

Title: AORTIC CROSS-CLAMPING: DOES IT ALTER RIGHT VENTRICULAR FUNCTION?

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Introduction

Acute increases in right ventricular afterload result in right ventricular decompensation. Application of the aortic cross clamp may be associated with changes in both right and left ventricular performance. Left ventricular decompensation is most likely to occur during aortic reconstructive surgery with application and release of the aortic cross-clamp (XC).[1] However, the response of right ventricle has not been documented during these periods. Therefore, we designed a study to evaluate right and left ventricular function during abdominal aortic surgery.

Methods

With approval of the Human Investigation Committee, ten patients (n=10) (mean age = 65 years) scheduled to undergo routine abdominal aortic surgery with cross-clamping were evaluated. Ninety minutes prior to arrival in the operating room, patients were premedicated with intramuscular morphine 0.1mg/kg and scopolamine 0.4mg. Intravenous and arterial catheters were placed percutaneously under local anesthesia. Induction was accomplished with fentanyl (30 μg/kg), and pancuronium (0.1 mg/kg) was used to provide muscle relaxation. For maintenance of anesthesia, isoflurane was titrated as clinically indicated. Ventilation was maintained using an $FIO_2 = 0.5$.

Hemodynamic measurements were recorded at the following designated intervals: baseline (pre-induction), post-surgical incision, immediately prior to XC application, one minute post XC application, ten minutes post XC application, immediately prior to initial release of XC, one minute after initial release of XC, immediately prior to final XC release, one minute after final XC release and at abdominal closure. Measurements obtained at end exhalation included: heart rate (HR), blood pressure (BP), right atrial pressure (RAP), right ventricular end diastolic pressure (RVEDP), mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO) and right ventricular ejection fraction (RVEF). RVEF (normal = 40%) was computed using diastolic plateaus of a thermodilution CO curve obtained with a rapid response thermistor Swan Ganz catheter.[2]

Data are expressed as mean ± SD. Analysis of variance and coefficient of correlation tests were used for data analysis with $p < 0.05$ considered significant.

Results

One hundred (n=100) hemodynamic profiles were obtained from ten patients (n=10). No significant alteration in right ventricular function was observed in our series of patients during surgery or at times of aortic XC application or release. The baseline RVEDP = 9 ± 2 mmHg did not significantly (p=NS) increase following application of the aortic cross clamp (Table I). Similarly, the baseline RVEF of 33 ± 3% remained unchanged (p=NS) throughout the study period. Likewise, no statistically significant alteration in left ventricular function, as assessed via PCWP, CO, or PAP, could be detected during or following the period of aortic cross clamping (Table II).

Discussion

Left ventricular dysfunction during aortic surgery occurs primarily in patients with pre-existing coronary artery disease and is common during the periods of aortic cross-clamping and at its release.[3] The data of our study, however, indicates that, even in patients with clinically significant cardiovascular disease, a reduction in RV performance, as evidenced by changes in RVEDP or RVEF is not a universal event. We have observed that in those patients in whom LV performance is unaltered by XC application, right ventricular performance also remains unchanged. In conclusion, it appears that alterations in right ventricular function are unlikely to occur during aortic surgery without evidence of simultaneous left ventricular dysfunction.

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TABLE I
RIGHT VENTRICULAR HEMODYNAMIC DATA
(n=10)
Mean ± SD

	RVEF (%)	RVEDP (mmHg)	PAP (mmHg)
Pre-ind.	33 ± 3	9 ± 2	18 ± 2
Pre XC appl.	32 ± 4	10 ± 3	17 ± 2
1 min post-XC appl.	34 ± 3	8 ± 2	17 ± 3
1 min post XC release	32 ± 3	7 ± 3	18 ± 3
Immed. prior to XC release	34 ± 4	7 ± 2	17 ± 3
Abdominal closure	34 ± 3	8 ± 2	17 ± 2

TABLE II
LEFT VENTRICULAR HEMODYNAMIC DATA
(n=10)
Mean ± SD

	HR (b/min)	BP (mmHg)	CO (L/min)	PCWP (mmHg)
Pre-ind.	64 ± 3	89 ± 5	6 ± 2	14 ± 2
Pre XC appl.	62 ± 2	84 ± 3	6 ± 3	13 ± 2
1 min post-XC appl.	66 ± 3	82 ± 4	6 ± 2	13 ± 3
1 min post XC release	71 ± 2	85 ± 3	6 ± 2	15 ± 2
Immed. prior to XC release	75 ± 4	84 ± 4	6 ± 3	15 ± 2
Abdominal closure	72 ± 3	85 ± 4	6 ± 2	14 ± 3

Title SIGHT AND SOUND: CAN DOUBLE-LUMEN ENDOBRONCHIAL TUBES BE PLACED ACCURATELY WITHOUT FIBEROPTIC BRONCHOSCOPY?

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Introduction

Failure of effective ventilation occurs if double-lumen endobronchial tubes (DLT) are malpositioned. Clinicians using DLTs have, in the past, relied solely on physical examination to confirm accurate placement. Recently, however, fiberoptic endoscopes have been used with increasing frequency, either to place the tube under direct vision or to check the position once the tube has been passed (1,2). We have designed a study to determine whether DLTs placed using clinical signs are in a satisfactory position when checked at subsequent bronchoscopy.

Methods

With approval of the Human Investigation Committee, 23 patients (mean age = 55 years) undergoing elective thoracotomy which required the use of DLTs were studied. Anesthesia was induced with sodium pentothal (4-6 mg/kg) and muscle relaxation obtained with succinylcholine (1 mg/kg). Following insertion of an appropriately sized polyvinyl DLT, the tracheal and bronchial cuffs were inflated. The ability to isolate each lung was then checked by alternatively clamping the tracheal and bronchial limbs and noting the presence or absence of chest movement in three areas of each hemithorax - apical, anterior and axillary. Similarly, auscultation was performed over these areas. Fiberoptic bronchoscopy (Machida ENT 4L-50) was then performed to check whether bronchoscopic findings confirmed clinical impressions of successful positioning. The ratio of correct positioning of the tube using clinical signs compared to the ratio of correct positioning with the tube using bronchoscopy was examined using the 95% confidence interval.

Results

Nine patients underwent right thoracotomy and 14 patients a left thoracotomy. Twenty-two patients received a left sided DLT. In all cases, selective isolation of each lung was possible, and, using clinical signs, each DLT was considered to be accurately placed. However, in 11 patients (48%) bronchoscopy revealed the DLT to be in an unsatisfactory position (confidence interval 28%-68% at $p < 0.05$). Bronchoscopic abnormalities are described in Table 1 and bronchoscopic views shown in figures 1 and 2.

Discussion

Burton et al. (3) have reported a low incidence of problems using PVC DLTs. However, in their study, bronchoscopy was not used to confirm correct positioning. Our bronchoscopic observations reveal that only 52% of DLTs are optimally placed using clinical criteria. In two cases (8%), malplacement resulted in ventilatory abnormalities. We suggest that fiberoptic bronchoscopy be used routinely to accurately confirm the position of DLTs.

Table 1: Abnormal findings on bronchoscopy (n = 23)

	No. of patients	%
Herniation of bronchial cuff over carina	4	17
Bronchial cuff not visualized	6	27
Narrowing of bronchial lumen of DLT	1	4

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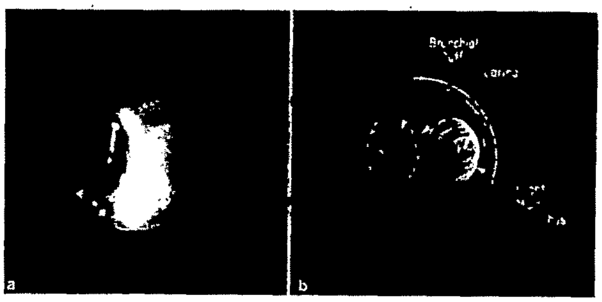

Fig. 1. View through endoscope showing correct position of bronchial cuff.

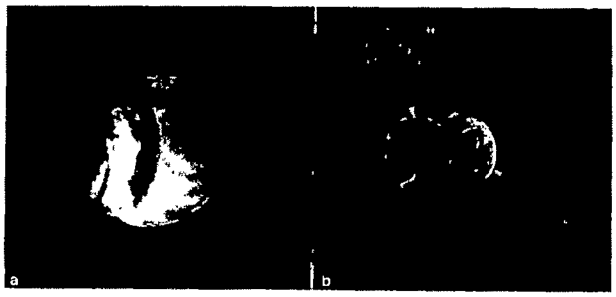

Fig. 2. View through endoscope showing herniation of bronchial cuff over carina.

Title: The EEGs of Alfentanil, Sufentanil, and Fentanyl: A Quantitative Comparison

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Introduction. We previously compared the EEG produced by high-dose fentanyl (F) or sufentanil (S) anesthesia, concluding that these agents markedly and characteristically alter the EEG, that the changes with F and S are similar, and that these changes should be useful for monitoring of narcotic anesthesia (1). The present study compares F and S with another narcotic agent, alfentanil (A).

Methods. The protocol was approved by the appropriate institutional human research committees, and written informed consent was obtained from each patient. F (58 mcg/kg) or S (9.1 mcg/kg) was given over the course of 5-10 min while A (150 mcg/kg) was given in 1 min. The only other agents used were oxygen, pancuronium, and metocurine. For the EEG we used 6 gold-cupped EEG electrodes on each patient; 2 each in the FP1-O1 and FP2-O2 positions and 2 as indifferent electrodes. The EEG was analyzed by aperiodic analysis (Neurometrics Monitor), and during sequential 30- or 60-sec epochs, total number of waves (TNW), total power at 1 Hz (TP1), cumulative % power at 3 Hz (CP3), and the frequency at a cumulative power of 90% (F90) were extracted (1). We performed analysis of variance and used the Bonferroni inequality for t-tests on the difference among peak values for the three opiate agents.

Results. Figures 1-4 compare the EEGs of F and S with that of A on an event scale. (C = control, OA = oral airway, F = Foley, L&S = laryngoscopy and spray, L&T = laryngoscopy and intubation, LI = leg incision, SI = sternal incision, SAW = sternal saw, SP = sternal split.) The EEGs are directionally similar, but tended to be different in magnitude and strikingly different in time course. A always showed greater maxima or minima than the other two agents, although occasionally the difference from the other two agents was small and/or not significant. Changes with A, as with F and S, tended to be more marked in the lower frequency range. Thus, the major A-induced changes were seen with TP1 and CP3, both of which increased considerably.

Discussion. The EEGs of the 3 fentanyl analogs were similar in pattern, although the peaks with alfentanil tended to be higher and the time course considerably faster, particularly on emergence. The qualitative EEG similarity among the fentanyl analogs suggested by these 4 variables is also seen in the greater detail of the color display on the Neurometrics or Lifescan EEG monitors. Two reasons could account for the greater changes with A: we gave relatively more A and injected that agent more rapidly. Under similar conditions, a more rapid injection would be expected to yield greater changes in plasma levels and tissue levels. Regarding the former, the potency ratio for F/A is 4.0-4.2 and for S/A, 20.8-25.7, while the respective dose ratios that we used were 2.6 for F/A and 16.5 for S/A. This suggests that we did indeed give relatively more A than either of the other two agents. Without concomitant brain levels, we can only speculate on whether the EEG reflects "depth of anesthesia" with opiates. The present results do strengthen the impression that the EEG at least qualitatively tracks brain concentrations of the opiates.

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1. Smith N Ty, Dec-Silver H, Sanford TJ, Westover CJ, Quinn ML, Klein F, Davis DA: Anesth Analg 63: 386-93, 1984.

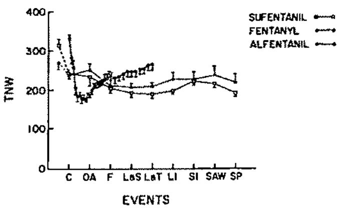

Figure 1. The EEG response to A, F, or S as demonstrated by TNW.

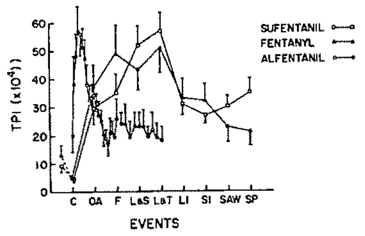

Figure 2. The EEG response to A, F, or S as demonstrated by TP1.

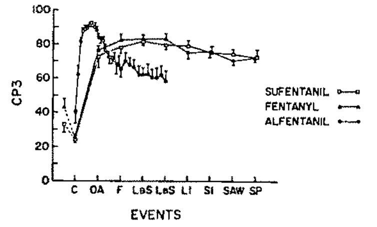

Figure 3. The EEG response to A, F, or S as demonstrated by CP3.

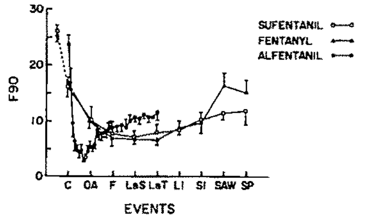

Figure 4. The EEG response to A, F, or S as demonstrated by F90.

Title: INDUCTION WITH THIOPENTAL OR ALFENTANIL: EEG EFFECTS

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Introduction: We compared the EEG effects of thiopental (T) with the new, rapidly acting narcotic alfentanil (A) following a single injection for the induction of anesthesia. A computerized technique, aperiodic analysis (1), quantified the EEG.

Methods: The protocol was approved by both University and Hospital Human Research Committees, and informed, written consent was obtained from each patient. In a randomized, double-blind design, we assigned 36 male patients into four groups of 9 each. Group I received 25 mcg/kg pancuronium followed in 2 min by A 150 mcg/kg and immediately by succinylcholine 1.5 mg/kg, while Group II received 100 mcg/kg pancuronium followed immediately by A. Groups III and IV were similar to I and II respectively, except that 4.0 mg/kg T was given. In all groups, the induction agent was administered over a one-minute interval. We continuously recorded FP1-01 and FP2-02 EEG leads into an analog tape recorder, before and for 90 min following induction. The EEG tape was played back into an aperiodic analyzer (Neurometrics EEG Monitor) and thence onto a floppy disk. From this we derived 30-sec epochs for 15 min following induction, each epoch containing 153 variables, from which we selected 4 and created 3: the total number of waves (TNW), total power at 1 Hz (TP1), total power at 4 Hz, (TP4), cumulative power at 3 Hz (CP3), TP10-12, average power at 17-19 Hz (AP17-19), and an "edge track" - the frequency below which 90% of the power resides (F90) (1). We used analysis of variance and the Bonferroni inequality, with P 0.05 defined as borderline significance.

Results: We combined the muscle relaxant groups, so that the results represent 18 patients for A and 18 for T. Every variable was affected drastically differently by the 2 agents. The results from 4 of the variables are shown in the figures. There were both quantitative and directional differences in the EEG responses to the two agents.

Discussion: All of the variables, including the ones not shown, illustrate several points. 1. A tended to be slower in onset and to last longer than T. 2. Both agents produce impressive changes in the EEG. 3. The EEG changes are different, and the differences are quantifiable. 4. T produces a biphasic response in the EEG, with respect to time. 5. A produces a monophasic response, with the time constants varying considerably from variable to variable. 6. As a corollary of #5, if one wishes to relate a quantitative EEG to serum or brain levels of A, one should choose the variables carefully before concluding that no relationship exists. 7. Low-frequency variables are more useful for assessing anesthetic depth with A, while higher frequency variables are more useful with T. 8. Some variables, such as CP3, which increases quickly and returns to baseline relatively slowly, should be useful to estimate the depth of anesthesia during low-dose A. Others, such as TP1, which rises more slowly but returns more quickly to baseline, should be useful mainly for high-dose A. This last point corroborates the conclusions drawn previously with fentanyl and sufentanil, using the same type of analysis (1).

Reference 1. Smith N Ty, Dec-Silver H, Sanford TJ, Westover CJ, Quinn, ML, Klein F, Davis DA: EEGs during high-dose fentanyl-, sufentanil-, or morphine-oxygen anesthesia. Anesth Analg 63:386-393.

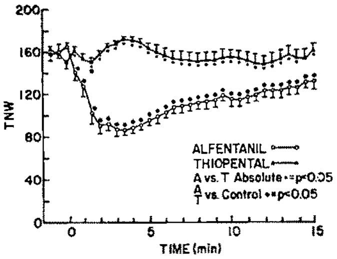

Figure 1. The EEG response to A or T as demonstrated by the total number of waves (TNW).

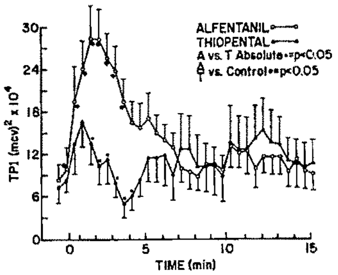

Figure 2. The EEG response to A or T as demonstrated by the total power at 1 Hz (TP1).

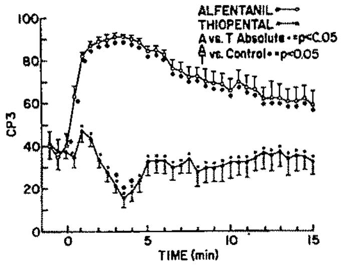

Figure 3. The EEG response to A or T as demonstrated by the cumulative power at 3 Hz (CP3).

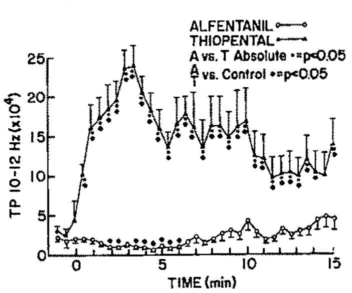

Figure 4. The EEG response to A or T as demonstrated by the total power at 10-12 Hz (TP10-12).

Title: COMPARATIVE EFFECTS OF ORAL SODIUM CITRATE AND ORAL CIMETIDINE ON GASTRIC pH IN PEDIATRIC PATIENTS

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Introduction:

Pulmonary aspiration of gastric contents remains a major hazard for anesthetized patients. 26% of anesthesia related mortality in pediatric patients has been attributed to aspiration of vomitus.[1] A pH below 2.5 and gastric volume in excess of 0.4 mg/kg are observed more frequently in children than adults. These are the limiting values for development of severe pneumonia after aspiration of gastric contents.[2] Oral cimetidine (10 mg/kg) given one to three hours prior to induction of anesthesia is effective in reducing both the acidity and the volume of gastric contents.[3] Recently, an oral nonparticulate antacid 0.3 M sodium citrate has gained popularity for aspiration prophylaxis. This study was done to assess the effectiveness of oral 0.3 M sodium citrate as compared to oral cimetidine in pediatric patients.

Methods:

The study was approved by the Institutional Review Board. Sixty ASA Class I patients between the ages 6 months to five years were randomly selected from elective operative schedule. Their weights were recorded. No preoperative medication was given. The study was double blinded and was divided into three groups of 20 subjects each.

Group I (control):	Received no medication.
Group II (citrate):	Received 0.4 ml/kg 0.3 M sodium citrate orally 30 minutes prior to induction of anesthesia. Sodium citrate was supplied by hospital pharmacist.
Group III (cimetidine):	Received 10 mg/kg of cimetidine orally sixty minutes prior to induction of anesthesia.

All children were anesthetized with inhalation induction. Choice of anesthetic was left to the anesthesiologist doing the case. Intravenous access was obtained. Appropriate dosages of atropine and succinylcholine were administered intravenously for endotracheal intubation. An orogastric tube was passed. Its position was confirmed by air insufflation and auscultation of left hypochondrium. Gastric contents were aspirated by pressing on the abdomen and following head down position. The pH of gastric contents was measured by Fisher digital pH meter and Fisher glass electrode. Volume of gastric contents was measured but not included in the study because of varied amounts of oral medication administered. The results were recorded and the data was analyzed using Dunnett's test. A $p < 0.05$ was considered significant.

Results:

There were 23 female and 37 male children. Mean age was 3.67 ± 0.09 years. Mean weight was 16.7 ± 0.02 kgm. Mean pH and standard deviations for three groups are shown in table 1.

TABLE 1

GROUP	N	MEAN GASTRIC PH	S.D.
CONTROL	18	2.15	1.16
CITRATE	20	5.26	1.68
CIMETIDINE	16	3.71	1.87

No sample could be aspirated in 2 patients in the control group and 4 patients in the cimetidine group. 90% of the control patients had a pH ≤ 2.5, whereas only 5% in the citrate group and 25% in the cimetidine group had a pH ≤ 2.5. Mean of the citrate group differs by 3.1 pH units from control and this is significant ($p < 0.001$). Mean of the cimetidine group differs by 1.56 pH units from the control ($p < 0.05$).

Discussion:

This study shows that sodium citrate is an effective oral antacid in pediatric patients. Stress and emotional upset increase gastric acid production. Risk of aspiration is theoretically present in all age groups with children being at the greatest risk. Gastric volume and acidity are also higher but decline as the age advances.[4] Special risk factors in pediatric anesthesia are short esophagus, frequent gastric air insufflation and dilatation, mask induction and uncuffed endotracheal tubes. Cimetidine is effective in an oral dose of 10 mg/kg. But this has to be administered one to three hours prior to induction of anesthesia.[2] Conversely, oral sodium citrate raises the gastric fluid pH within 30 minutes. Cimetidine has certain drug interactions unlike sodium citrate. This holds special reference for pediatric population undergoing emergency surgery. We feel that 0.3 M sodium citrate alone is sufficient to alter gastric pH.

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Title: Comparison of Atracurium with d-Tubocurare for Prevention of Succinylcholine Myalgias

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Affiliation: Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania 19107

Introduction: Atracurium bresylate (ATR) is a new intermediate acting non-depolarizing muscle relaxant. While it has been extensively investigated, we are aware of no study testing its efficacy in attenuating postoperative myalgias (POM) after succinylcholine (SDC) administration. The following study was designed to compare ATR and d-Tubocurare (DTC) given prior to SDC for intubation and to correlate the occurrence of outpatient POM, and fasciculations.

Methods: After approval by the Human Research Subjects Committee, forty-four ASA Class I or II females with ages ranging from sixteen to fifty who were undergoing outpatient laparoscopy were selected. The patients were free from neuromuscular, hepatic, cardiovascular and renal disease. There were no apparent anatomic abnormalities which would contribute to difficult endotracheal intubation. The subjects were assigned to three groups: Group 1 received 0.025 mg/kg ATR; Group 2 received 0.05 mg/kg DTC and Group 3 received saline (NS) in a double blind manner. Pentothal Sodium was administered at 1 minute 45 seconds after pretreatment in doses to allow control of ventilation. The ulnar nerve was stimulated with impulses of 0.2 msec. duration and supramaximal amplitude at 1 Hz after induction and the resultant thumb twitch was noted. Three minutes post pretreatment administration, SDC 1.5 mg/kg was administered to all patients and fasciculations when present, were noted on the following scale: Nil (0); mild fine fasciculations of the eyes, face, neck or fingers without limb movement (1); moderate fasciculations of greater intensity than mild occurring at more than two sites or limb movement (2); severe vigorous, sustained and widespread fasciculations possibly requiring forceful retention (3).

Patients were intubated when maximum paralysis was noted. All patients were contacted one and three days post-operatively and were questioned to disclose POM by the following scale: Absence of pains or characteristic post-laparoscopic gas pains (0); mild muscle stiffness or pains, on specific questioning, in the nape of the neck, shoulders and lower chest on deep breathing (1); moderate muscle stiffness and pains complained of by the patient spontaneously requiring analgesics (2); severe incapacitating generalized muscle stiffness or pain (3). Multivariate analysis of variance followed by Duncan's multiple range test was performed to detect any significant difference in dependent variables between the groups. The relationship between POM and fasciculation was determined by Pierson product moment correlation. A $p < 0.05$ was considered significant. All results are expressed as Mean (± SD).

Results: The results of the study are summarized in Table 1. Intubating conditions were adequate in all cases. The time to maximum relaxation, as determined by thumb twitch, did not vary significantly among the groups. All patients were discharged from the hospital on the day of surgery. Fasciculations were significantly less in the ATR and DTC groups than the NS group. Myalgias on the first postoperative day were significantly reduced in the ATR group as compared to the NS group. There was no significant difference between the DTC and NS groups in this regard. On the third post operative day POM were rare and there were no significant differences between the groups. There was no relationship between fasciculations and POM.

Discussion: In a pilot study of 20 inpatients we found almost no POM with the same protocol described above (unpublished results). Churchill-Davidson[1] and others have noted that POM is most often seen in ambulatory patients. Newman and Loudon[2] noted that POM is more common in females. Finally Brodsky and Ehrenwerth[3] stressed the importance of standardizing the surgical procedure in discussing POM. We feel that our patient group readily satisfies these criteria.

The doses of ATR and DTC were 10% of their ED_{95}. This study confirms the efficacy of DTC in decreasing fasciculations after SDC and identifies ATR as an alternate of equal value. We also confirm the findings of Brodsky and Ehrenwerth[3] and others[4] that "the presence of fasciculations was not related to the occurrence of muscle pains"[3]. The significant reduction in POM on day 1 demonstated by ATR suggests that this agent should be evaluated as the drug of choice for this property.

TABLE 1

Group	1 (n=13)	2 (n=17)	3 (n=14)
Pre-fasciculant	ATR[1]	DTC[1]	NS[1]
mg/kg	0.025	0.05	-
Fasciculations[2]	0.61±0.77	0.18±0.52	1.21±0.80
POM[3] (Day 1)			
% of patients	15	41	57
Score	0.15±0.37	0.47±0.62	0.68±0.72

[1] injected 3 minutes before SDC 1.5 mg/kg.
[2] score-(See text) [3] post-operative myalgias

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Title: Priming with Atracurium - A Clinical Trial

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Introduction: Recently a new dosing method for facilitating rapid tracheal intubation with non-depolarizing muscle relaxants has been proposed.[1-3] This method, known as the priming principle (PP), utilizes a small dose of non-depolarizer prior to induction with the administration of a second larger dose later. An appropriate priming dose would allow patients to maintain adequate respirations, protect their airway and be subjectively acceptable. In this study we evaluated the PP with Atracurium (ATR).

Methods: 39 adult female ASA Class 1 and 2 surgical patients took part in this study. Following the measurement of maximum inspiratory pressure (MIP) patients were randomly assigned to either of two treatment groups in a double blind manner. Group 1 (n=18) received an IV bolus of normal saline (NS), while Group 2 (n=21) received ATR 0.060 mg/kg, while awake. After 3 ½ minutes, the patients were asked to lift their head for 5 seconds and MIP was measured again. Pentothal sodium was administered in sufficient quantities to establish controlled ventilation by mask 4 minutes after the first syringe was injected. At five minutes Group 1 received ATR 0.360 mg/kg. and Group 2 received ATR 0.300 mg/kg.

After the pentothal, a DigiStim II nerve stimulator (Neuro Technology, Inc., Houston, TX) was used to stimulate the ulnar nerve with supramaximal impulses of 0.2 msec. duration at 2 Hz through subcutaneous needles. The train of four stimuli were repeated every ten sec. The resulting thumb twitch was measured using a Grass FT03C force displacement transducer and recorded on paper with a Grass Polygraph. 90 seconds after the final relaxant dose, intubation was attempted by an experienced laryngoscopist. Conditions for intubation were graded on the following scale: 4-Easy and no reaction; 3-Vocal cord movement present, jaw incompletely relaxed; 2-Vocal cord movement and moderate reaction; 1-Impossible without supplemental time. ANOVA and Fisher exact probability test were performed to detect any significant differences. A $p \leq 0.05$ was considered significant. All results are expressed as mean (± SD).

Results: The results of the study are summarized in Table 1. There was no significant difference between the groups in terms of age or weight. One patient in each group could not be intubated at 90 seconds. The PP group had a T^4/T_1 ratio of 0.51 (0.23) at 90 sec. while with NS/ATR it was 0.73 (0.14). This was statistically significant ($p < 0.001$). MIP decreased in 8 patients in the PP group as compared to none in the NS/ATR group. This was statistically significant ($p < 0.005$). There was no significant difference between the 2 groups with respect to intubating conditions, % of patients bucking at intubation, time to maximal relaxation and time to recovery to 20% of initial twitch height. Four patients in the PP group could not sustain head lift prior to induction as compared to none in the NS/ATR group. However this was not statistically significant.

Discussion: The PP was recently reported to hasten the onset of good intubating conditions with vecuronium preceded by a priming dose of vecuronium[1], or ATR preceded by a priming dose of either pancuronium, metocurine or d-tubocurarine[2]. However, these studies either did not examine the effects of the priming dose on awake patients[1,3] or did not have a suitable control.[2] In a pilot study, we attempted to determine the maximum priming dose that would be tolerated by awake patients. We found that 36% of patients receiving 0.070 mg/kg ATR could not tolerate this dose, as determined by ability to sustain head lift (unpublished results). The present study shows that the incidence of this adverse reaction can be reduced to 19% (4 in 21) by reducing the dose to 0.060 mg/kg. At this dose 38% of the PP patients showed decreased MIP and many had subjective complaints.

A total dose of 0.360 mg/kg was chosen since we noted that although most patients could be successfully intubated at 90 sec., conditions were far from optimal and any improvement provided by the PP would be obvious.

This study clearly shows that the PP with ATR, while providing a small improvement in T^4/T_1 ratio at intubation, does not significantly improve intubating conditions. It is complex, time consuming, is not well tolerated and may put patients at risk for aspiration.

Table 1

Group	1 (n=18)	2(n=21)	p
Muscle Relaxant* (mg/kg)	NS/ATR -/0.36	ATR/ATR (0.06/0.30)	-
Conditions at ‡ intubation	3.4 (0.84)	3.7 (0.80)	**
% Bucking on intubation	72	62	**
T_4/T_1 ratio at 90 sec.	0.73 (0.14)	0.51 (0.23)	<0.001
% of patients able to sustain head lift	100	81	**
% of patients showing decreased MIP	0	38	<0.005
Time to max. twitch depression, min.	6.3 (3.1)	6.5 (3.4)	**
Time to 20% recovery of initial twitch, min.	26.4 (6.0)	24.6 (9.3)	**

* injected 5 minutes apart; ‡ Score (see text)
** not significant

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Title: INCIDENCE OF VENOUS AIR EMBOLISM IN TOTAL HIP ARTHROPLASTY

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Introduction: Venous air embolism (VAE) is a complication of many surgical procedures including craniotomy, hepatectomy, pelvic surgery and total hip arthroplasty.(1) The incidence during sitting craniotomy has been described as up to 40 percent with over half of those occurences with hypotension or cardiac arrhythmias.(2) VAE may be clinically non-evident or may cause a gradation of hemodynamic changes dependent upon the amount of air embolized, the rate of embolization, and the anatomical structures involved with the embolus. Emboli may lodge in the right heart or pulmonary vasculature, causing hypotension, pulmonary edema, arrythmias, and hypoxemia.(1)

In one study, six patients were monitored for VAE during total hip arthroplasty (THA).(3) Five patients developed Doppler changes characteristic of VAE and four had air retrieved from a central line. This study reports preliminary data from a series being conducted to find the incidence of VAE during THA.

Methods: This study was approved by the institutional human investigation committee. Eighteen patients gave informed consent and were included in the study. All patients were pre-medicated and anesthetized according to the practice of the anesthesiologist and in accordance with the patients' pre-existing diseases. Anesthetic techniques included 13 cases of combined epidural and inhalational anesthesia, 4 inhalational anesthesia, and 1 caudal anesthesia with sedation. All patients were monitored in the usual manner with the addition of direct radial arterial pressure monitoring, central venous pressure (CVP) or pulmonary artery catheter monitoring (PA), pre-cordial Doppler ultrasound (Med-sonic Versatone Doppler Model Number 8) and mass spectrometry gas analysis. Data included: vital signs, arterial blood gases, end tidal nitrogen, end tidal carbon dioxide, and CVP or PA pressures measured at least four times during the surgery. The collection times were: 1) post intubation, 2) after placement of the acetabular component, 3) after placement of the femoral component, 4) at the time of closure. A complete data set was collected again if the Doppler or other monitoring was suggestive of VAE. Aspiration of the CVP or PA catheters for air was also carried out if VAE was suspected. Doppler sounds were graded subjectively by the investigators as one to three plus. Associated surgical maneuvers were noted whenever VAE occurred.

Results: Eleven of the 18 cases monitored had at least one episode suggestive of VAE by Doppler. Seven of these eleven cases (64%) exhibited one or more transient hypotensive episodes concomitant with Doppler changes. One hypotensive episode resulted in a blood pressure decrease to 50/30 mm Hg. All hypotensions responded to fluid and catecholamine therapy. Three cases (27%) had arrhythmias during Doppler changes, two with premature atrial contractions, and one with brachycardia. Arterial blood gases showed an increased carbon dioxide in one patient during suspected VAE by Doppler. Aspiration of air from the central line, elevation of CVP and changes in end-tidal nitrogen or carbon dioxide all occurred in one patient each with abnormal Doppler sounds.

The eleven patients who had changes consistent with VAE had a total of twenty separate events. The correlations with surgical maneuvers are noted in Table 1.

Table 1 Surgical Maneuvers at the Time of Doppler Event (VAE)

Femor Preparation - 5
Femoral Component Placement - 5
Acetabular Preparation - 4
Anatomical Realignment of Leg - 4
Removal of old prosthesis - 1
Cement Placed in Femor - 1
(N = 20 events)

Discussion: Transient hypotensive episodes during THA have been well described. These events have been previously attributed to the cardiovascular effects of methylmethacrylate monomer.(4) VAE has been reported in multiple types of surgeries but there are no large series reporting its incidence in THA. This preliminary report shows a high (61%) incidence of VAE at multiple times during surgery (see Table 1). VAE may be responsible for some hemodynamic changes previously attributed to methylmethacrylate monomer. The Doppler ultrasound was the most sensitive monitor for VAE. The high incidence of VAE and the major cardiovascular changes during THA found in this series supports the usage of hemodynamic monitoring, Doppler ultrasound monitoring and mass spectrometry.

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Title: NIFEDIPINE INDUCED HYPOTENSION IN MAN: ENDOCRINE RESPONSE DURING ISOFLURANE AND HALOTHANE ANESTHESIA

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Introduction. One of the characteristics of the calcium channel blocker nifedipine (N) is its ability to reduce blood pressure with little change in cardiac output (1). No data are available concerning the stress response to N-hypotension during anesthesia and surgery. The purpose of this study was to quantitate the pattern of circulating catecholamines, plasma renin activity (PRA), ß-endorphin (ß-END) and cortisol (CORT) in response to N-induced hypotension.

Methods. 20 patients (ASA I, II, mean age 35 yrs), scheduled for maxillofacial surgery, gave informed consent to the institutionally approved protocol and were randomized in two groups to receive either isoflurane (I; n = 10) or halothane (H; n = 10) anesthesia. Each patient was premedicated with flunitrazepam (0.03 mg/kg p.o.). Radial arterial and pulmonary arterial catheters were inserted under local anesthesia. After control measurements (C), anesthesia was induced with thiopental 5 mg/kg and succinylcholine 1 mg/kg for intubation. Anesthesia was maintained with 1.2 MAC I or H, N_2O/O_2 (4:2 l/min) and alcuronium 0.2 mg/kg. Ventilation was controlled and an i.v. bolus of 0.1 mg/kg metoprolol was given for ß1-blockade. After measurements were taken during steady state anesthesia (A), hypotension was induced with N (20 µg/kg bolus, maintenance-infusion 3 µg/kg/min) and measurements repeated after 20 (H1) and 90 (H2) min. Surgery started after H1-measurements. Blood was analyzed for plasma catecholamines (HPLC), PRA (RIA), ß-END (RIA; 2), cortisol (RIA), N-plasma levels (HPLC), gases and electrolytes. All data were evaluated by analysis of variance for repeated measures with the Bonferroni t-test (significance level $p < 0.05$).

Results. Data are presented in the figure. There were no significant differences between the 2 groups. The combination of anesthesia and ß-blockade (A) produced a significant drop in MAP (I: 26%; H: 20%). The N-induced hypotension was associated with a further decrease in MAP (I: 28%; H: 31% from A). Epinephrine (EPI) showed a 3-fold drop from C to A and returned to C-levels during N-hypotension. Norepinephrine (NE) and PRA-levels increased continuously up to 6- and 12-fold, respectively, after 90 min hypotension and surgery. ß-END remained unchanged until H1 but a 2.5-fold increase was noticed after 90 min of hypotension. This ß-END elevation reached significance only in the H-group. The CORT profiles – although similar – were not significant.

Discussion. This study confirms the drop of EPI during inhalation anesthesia. NE-concentration is considered to be an index of the activity of the peripheral sympathetic nervous system (SNS). It is well known that a fall in MAP induces reflex activation through the arterial baroreceptors of the SNS. Additional mechanisms may account for the high NE-levels: bolus of ß-blocker initially increase plasma catecholamines; ß-blocker and hypotension reduces the systemic clearance of catecholamines in lung and liver (3). The pronounced increase in PRA in comparison to NE cannot be explained solely by the activation of the SNS. The enhancement of PRA is mediated additionally by nonneural mechanisms controlled by the renal perfusion pressure (4). We did not observe changes in ß-END during anesthesia and the early phase of hypotension confirming others (5). In contrast, we were unable to find any change in CORT-levels during I- or H-anesthesia with N_2O (6). The increase in both ß-END and CORT at H2 may indicate a common stimulus, which becomes apparent only during prolonged hypotension.

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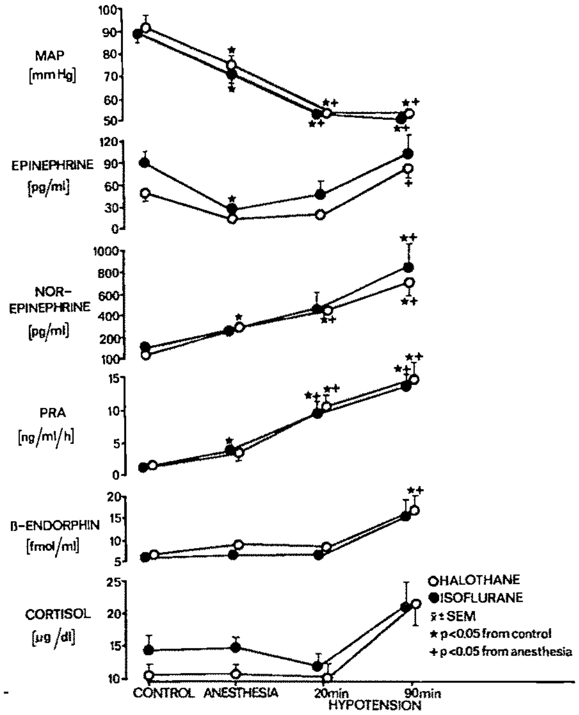
Figure.



Title: EFFECT OF EPIDURAL ANESTHESIA ON RESTING METABOLIC RATE (RMR)

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Introduction. Although there are numerous studies showing that the commonly used general anesthetics depress resting metabolic rate (RMR) (1,2), there is a lack of a well controlled study of the effects of thoraco-lumbar epidural anesthesia on RMR in man. It has also been reported that RMR is elevated the morning of surgery when compared totrue basal metabolic rate measured some days prior to surgery (3). This study was designed to examine both of these points: (a) Is resting metabolic rate elevated the day of surgery; and (b) Does epidural anesthesia alter resting metabolic rate?

Methods. Following approval of the appropriate institutional review boards, and with the informed consent of the patients, the following study was undertaken. Patients - age 18 to 70, scheduled for elective total hip replacement, with no evidence of cardiac dysfunction, and who were not receiving hormonal supplementation - were admitted to the Clinical Research Center two days prior to their surgery. RMR was measured by indirect calorimetry the day prior to surgery, and the day of surgery before and after T4-S5 epidural anesthesia had been achieved with 0.5% bupivicaine. Indirect calorimetry was measured using a ventilated hood system. Gas flow through the hood was adjusted to maintain a mixed expired carbon dioxide concentration of 0.5 to 0.7%. Mixed expired gases were continuously measured for flow (Vertek VR4500 pneumotachograph), oxygen content (Applied Electrochemistry S-3A fuel cell analyzer), and carbon dioxide concentration (Applied Electrochemistry CD-3A infra-red analyzer). Analyzer outputs were read every 6 seconds by a Hewlett-Packard 85 computer, and mean values for $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and R.Q. (STPD) for each 5 minute period were printed and stored. Three collection periods were averaged for each measure of RMR. Data were analyzed by analysis of variance.

Results. Six women and one man, with an average age of 60 years, an average weight of 81.8 kg, and an average surface area of 1.90 meters square participated in the study. Resting oxygen consumptions are listed below:

	Day 1	Day 2 pre-epidural	Day 2 epidural
$\dot{V}_{O_2}$	123 ± 6	122 ± 5	127 ± 6

Data are expressed as mean ml O_2/min/m^2 consumed ± S.E.M. There were no significant differences.

Discussion. These data fail to demonstrate any significant difference in resting metabolic rate the morning of surgery when compared to the preceding morning. When compared to data in the literature (3) these metabolic rates are consistent with what most authors call basal metabolic rates. All of our patients appeared relaxed and comfortable and had not received any premedication. Thus we would conclude that an adequate estimate of RMR and basal metabolic rate can be obtained the morning of surgery. In addition thoraco-lumbar epidural anesthesia was not associated with a significant change in RMR. This is consistent with the data of Ottesen (4)on thoracic epidural anesthesiain healthy volunteers. We conclude that epidural anesthesia has minimal effects on RMR in the well hydrated, relaxed individual.

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Title: HOW FAST DOES CO_2 REALLY RISE DURING APNEA?

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Introduction. The rate at which $PaCO_2$ increases is important when caring for apneic patients. Past experiments examining the rate of rise of $PaCO_2$ were performed while oxygen was insufflated into the tracheas of anesthetized animals or humans. This investigation determined the CO_2 rate of rise during apnea when there was no gas flow into the lungs.

Methods. After Human Subjects Committee approval, 20 healthy, consenting adults breathed 100% O_2 through an anesthesia circle system with an infrared CO_2 analyzer between the mouthpiece and the Y-piece. The subject took 3 deep breaths to wash N_2 out of the lungs. Baseline end-tidal CO_2 ($ETCO_2$) was recorded after 30 sec of quiet breathing. Next, the subject held his breath at passive end-exhalation, or functional residual capacity (FRC), for 10 sec, and then exhaled fully through the CO_2 analyzer. The subject breathed O_2 quietly until $ETCO_2$ returned to the control value. This sequence was repeated after 20 sec and again after the subject's longest voluntary period of apnea. The majority of subjects could not breath-hold at FRC for more than 90 sec, and those that could, had an insufficient volume of gas remaining in their lungs to obtain a reliable $ETCO_2$. A logarithmic function relating duration of apnea and $ETCO_2$ was derived for these data.

A similar protocol was followed where subjects held their breath after inspiring deeply to total lung capacity (TLC). The same 20 subjects each held a deep breath 30 and 60 sec, and then as long as possible, exhaling completely through the CO_2 analyzer at the end of each period. Least squares linear regression analysis and a Pearson correlation coefficient relating $ETCO_2$ and duration of apnea were determined for these data.

Results. The mean $ETCO_2$ at which subjects could no longer remain apneic was 53 ± 6 mmHg after breath-holding at end-exhalation and 53 ± 4 mmHg after a deep breath. The equation (figure):

$$ETCO2 = 7.4 (\log [\text{apnea-time}]) + 39$$

described the relationship between $ETCO_2$ and duration of apnea during breath-holding at FRC. When subjects held their breaths at TLC, intersubject variation was too great to allow complex mathematical analysis. A linear regression of these data estimated the average CO_2 increase over time:

$$ETCO2 = (.12\ \text{mmHg/sec} \times \text{apnea-time}) + 40\ \text{mmHg}.$$

Discussion. Although $ETCO_2$ is not precisely equal to $PaCO_2$, changes in $ETCO_2$ accurately reflect $PaCO_2$ changes when subjects are hemodynamically stable. Therefore, $ETCO_2$ was a valid, noninvasive method by which to examine the rate of $PaCO_2$ change in healthy subjects. Clinically, apnea occurs at FRC, not TLC. Hence, breath-holding after passive exhalation more closely approximates the clinical situation. The CO_2 rate of rise during this condition was 7.2 ± 2.5 mmHg ($\bar{X}$ ± SD) during the first 10 sec of apnea, 2.1 ± 1.3 mmHg for the next 10 sec, and 1.0 ± .6 mmHg/10 sec intervals for the remainder of the 90 sec study period. With increased lung volume, more protracted breath-holding was possible, but it also diluted CO_2 in the lungs, so that the increase in CO_2 was reduced to 7 mmHg/min and probably underestimated $PaCO_2$ rate of rise during clinical apnea. The logarithmic rise in $ETCO_2$ with time likely was due to rapid release of CO_2 from the vessel-rich, metabolically active tissue, followed by slower release from these and other CO_2 stores. It is commonly believed that $PaCO_2$ will increase approximately 3 mmHg/min in apneic patients. Our results are probably different due to lack of gas insufflation and the awake state of our subjects. In conclusion, the increase in $PaCO_2$ during apnea is probably much more rapid than previously thought and rises logarithmically with time.

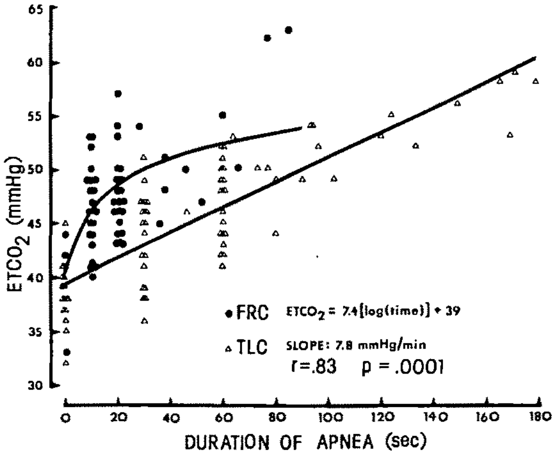

Figure. Duration of apnea and $ETCO_2$ at FRC (•) and TLC (△).

Title: EVIDENCE OF PARTIAL RECALL DURING GENERAL ANESTHESIA

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Introduction. The incidence and causes of recall under anesthesia are subjects of controversy. It is often assumed that the degree of recall of events occurring during general anesthesia is directly related to depth of anesthesia. However, patients who are apparently adequately anesthetized have experienced such recall.[1] In contrast, Terrell et al.[2], utilizing hypnosis, was unable to obtain evidence of recall of tape recorded information presented to patients under general anesthesia. The purpose of the present study was to determine if the presentation of uncommon words during general anesthesia would increase the frequency of their recognition postoperatively.

Methods. Approval was obtained from the Veterans Administration Human Studies Committee. Twenty-two ASA I-III male volunteers were studied with informed consent. A test was performed prior to induction to assure the patient's ability to hear tape recorded words through earphones. A randomized, double-blind study utilized a standardized anesthetic protocol. It consisted of glycopyrrolate 0.2 mg IV and diazepam 0.07 mg/kg IV followed 20 min later by a defasiculating 3 mg dose of d-tubocurarine, induction with thiopental 6 mg/kg IV and intubation with succinylcholine 2 mg/kg IV. Baseline recordings (Pre) obtained 2 min after induction included nasopharyngeal temperature (TEMP), heart rate (HR), mean arterial pressure (MAP), EEG mean zero-crossing frequency (ZXF) and end-tidal CO_2 (see Table). These measurements were used to define the patients' initial response to surgical anesthesia. A similar anesthetic response was maintained with 50:50 N_2O/O_2 and isoflurane. End-tidal isoflurane concentration was monitored continuously with an infrared analyzer. Subjects with an isoflurane exposure of greater than 4 MAC-hr were excluded from the study. Physiological measurements were also made after the initial surgical stimulus (Post). At this time 30-min-tape recordings consisting of repetitions of either 6 nonsense words (CONTROL group, n=10) or 6 very uncommon English words (EXPERIMENTAL group, n=12) were presented via headphones. After the completion of the taped presentation, the patients' ears were occluded for the remainder of general anesthesia. Within 48 hrs after anesthesia the patients were asked to choose the six words most familiar to them from a list of 36 uncommon words. A tape recorded message instructed the patients and pronounced each of the words. The frequency of recognition of each of the 36 words was compared in the 2 groups by analysis of variance.

Results. The mean age of the CONTROL group was 58 years (range 31-71) compared to 50 (range 26-78) for EXPERIMENTAL subjects. Mean isoflurane exposure was 2.1 ± 1.0 MAC-hr in the CONTROL group and 1.8 ± .9 MAC-hr in the EXPERIMENTAL group. The frequency of recognition of the 6 words presented intraoperatively was significantly greater in the EXPERIMENTAL group (F=10.16, df 1,20, P=.004). However, no subject had conscious recall of any intraopertive event.

Discussion. This study supports the view that the ability to hear and process information is not totally suppressed during deep general anesthesia. Our findings are thus in agreement with those of Millar and Watkinson.[1] These authors noted that reliance upon patients' spontaneous recall underestimated the poential for retention. Thus, both studies indicate the potential value of minimizing patient exposure to disquieting information during surgery.

Acknowledgements. This study was supported in part by the Veterans Administration Medical Center, Louisville, Kentucky. DATEX Instrumentarium Oy and Puritan-Bennett Corp. provided the Anesthesia and Brain Activity Monitor (ABM) and Anesthesia Agent Monitor (AAM).

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Table 1. PHYSIOLOGICAL RESPONSES TO STANDARDIZED ANESTHESIA

	TEMP (°C.)	HR (bpm)	MAP (mmHg)	ZXF (Hz)	CO_2 (torr)
CONTROL					
Pre	36	86	92	8	34
Post	36	91	81	7	32
EXPERIMENTAL					
Pre	36	93	100	8	36
Post	36	86	81	7	33

Title: CORRELATION OF ENDOTRACHEAL TUBE SIZE WITH SORE THROAT AND HOARSENESS FOLLOWING GENERAL ANESTHESIA

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Introduction. Following general anesthesia administered via an endotracheal tube, sore throat and hoarseness are the most common patient complaints. Cuff size and shape, cuff pressures, use of lubricant, and methcd of tube sterilization have all been shown to have some bearing on the frequency of these complaints. The effect of tube size on this frequency has not previously been examined. Since recent work has established that larger tube sizes exert higher pressures at the tube-mucosa interface, we hypothesized that small endotracheal tubes would result in less laryngeal damage and in fewer complaints of sore throat and/or hoarseness.

Methods. After obtaining approval from the University of Washington Human Subjects Committee and informed consent from the patients, postoperative sore throat and hoarseness were evaluated in 101 adults ages 17-85. All patients underwent orotracheal intubation for surgical procedures not involving the head or neck and not requiring placement of a nasogastric tube. Patients were randomly assigned to have their tracheas intubated with either a large (L) or small (S) tube. In males, a 9.0 mm inner diameter PVC tube (Portex, Inc., Wilmington, MA) was the L tube and a 7.0 mm was used as the S tube. In females, the L and S tubes were 8.5 mm and 6.5 mm, respectively. No lubricant was used and cuffs were inflated to a volume 1 ml above that needed to prevent gas leak at 35 cm H_2O pressure, with the cuff volume checked hourly. Patients were informed that tube size was randomized but were unaware of the objectives of the study. Each patient was interviewed 24-48 hours after the end of anesthesia by one of the authors who was unaware of the tube size used. Hoarseness and sore throat were graded on 0-3 scales as follows: Sore throat: 0 = none, 1 = less severe than with a cold, 2 = similar to that noted with a cold, 3 = more severe than with a cold. Hoarseness: 0 = none, 1 = noted by patient, 2 = obvious to observer, 3 = aphonia. Comparisons between groups were performed using the Mann-Whitney U test.

Results. Sixty-six males and 35 females were studied, reflecting the population seen at our hospital. There were no differences between the L and S groups in age, type of anesthetic, length of procedure, smoking history, or difficulty with intubation. The only complication apparently due to tube size was inability to pass the L tube in one female patient. Sore throat occurred in 22% of the S group and 48% of the L group, with the severity of the complaints as tabulated in Table 1 ($p < 0.002$ for S vs. L group). The relative frequencies of sore throat were similar in males and females, 22% in both for S tubes, 45% for L tubes in males and 53% for L tubes in females. Thirty-three percent of patients intubated with L tubes were hoarse compared to 18% of S tubes ($p < 0.05$), with more severe symptoms in the L group (Table 2). Females complained of hoarseness more than twice as frequently as males -- 37% vs. 18% ($p < 0.05$), with an incidence of hoarseness of 47% when an L tube was used vs. 28% with an S tube ($p = 0.08$). The comparable figures in males were 24% and 14% ($p = 0.13$).

Discussion. With routine short-term oral intubation for general anesthesia, smaller endotracheal tubes produced significantly fewer complaints of sore throat and hoarseness and did not produce morbidity due to their higher resistance or due to tube obstruction from secretions or kinking. We conclude that while the tube sizes used were all safe, patient satisfaction was greater with smaller tubes. We recommend the use of tube sizes in the range of our S tubes when not contraindicated by the presence of copious or thick secretions or by the need for a low-resistance airway.

Table 1. Sore Throat Severity

	0	1	2	3
S	43	11	1	0
L	24	16	6	0

Table 2. Hoarseness Severity

	0	1	2	3
S	45	8	2	0
L	31	8	7	0

We thank the residents and faculty of Harborview Medical Center for their assistance, and John Eiler for his statistical advice.

Title: THE EFFECTS OF TECHNIQUE AND SUPPLEMENTS ON CARDIOVASCULAR DYNAMICS DURING ANESTHETIC INDUCTION WITH ALFENTANYL

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Introduction. Large doses of alfentanil (150-250 µg/kg, IV) produce a rapid onset of unconsciousness, have a short duration of action and result in little change in cardiovascular dynamics, even in patients with marginal cardiovascular reserve. Because of these properties, alfentanil (ALF) has been proposed as an anesthetic induction agent, especially in patients with cardiovascular disease. However, there are some reports of profound decreases and increases in arterial blood pressure during induction of anesthesia with alfentanil in patients with impaired cardiac function.[1,2] We wondered whether the speed of administration of ALF, premedication with a belladonna (atropine), or benzodiazepine (diazepam) or pretreatment with pancuronium could prevent or cause hypotension or hypertension during induction of anesthesia with alfentanil. Thus this study was designed to evaluate induction of anesthesia with alfentanil in a sufficient number of patients with limited cardiovascular reserve to compare hemodynamics during: fast or slow administration of ALF; with or without premedication with atropine and/or diazepam; and with or without pretreatment with pancuronium.

Methods. The study was approved by the institutional human research board and permission obtained from 160 ASA Class II-IV patients with impaired cardiovascular function at the time of the preoperative visit. Patients were randomly assigned to 1 of 16 groups (10 pts/group) based on all possible combinations of the following: ALF administration rate (30 sec = fast; 3 min = slow); presence or absence of diazepam (0.1 mg/kg, PO) and/or atropine (0.4 mg, IM) premedication administered 60 min prior to induction of anesthesia; and presence or absence of pretreatment with pancuronium (1 mg, IV) 3 min prior to anesthetic induction. All patients had intravenous and intraarterial catheters inserted and a lead II EKG started upon arrival in the operating room. After a 5 min period of stablization, 3 min of breathing 100% oxygen and recording of baseline heart rate (HR) and systolic arterial blood pressure (SBP), 150 µg/kg of ALF was infused at the prescribed rate. If patients were still conscious 1 min after injection of ALF the infusion was continued (at the same rate) until they were unconscious (non-responsive to verbal and tactile stimulation) when succinylcholine (1.5 mg/kg) was given and the trachea intubated. Repeat measurements of SBP and HR were recorded when patients were unconscious, and every min for 10 min after endotracheal intubation. Data were analyzed for statistical significance using repeated measures analysis of covariance. The study design was a balanced 2 x 2 x 2 x 2 factorial layout.

Results. ALF produced unconsciousness in all patients. However, significantly lower amounts were required when the drug was given slowly, over 3 min (171 ± 5.6 vs 198 ± 7.0 µg/kg; p = 0.0027). Diazepam premedication also lowered the ALF sleep dose (175 ± 5.6 vs 195 ± 7.2 µg/kg, p = 0.0254) as did increasing age (< 40 yrs = 200 ± 10.8; 40-60 yrs = 196 ± 8.6; > 60 yrs = 168 ± 4.8 µg/kg; p = 0.0389). Anesthetic induction with ALF was often associated with wide fluctuations (marked increases in some patients and decreases in others) in systolic blood pressure (p = 0.0000) and heart rate (p = 0.0000) (Table 1 & 2). Neither hypotension nor hypertension, tachycardia or bradycardia were correlated with speed of infusion, dose of ALF, pretreatment or absence of pancuronium or premedication with atropine. However, premedication with diazepam, even though administered orally 60 min prior to induction, was associated with a significantly lower baseline SBP and lower SBP throughout the induction-intubation sequence.

Conclusion. Our results confirm that induction of anesthesia with ALF is often associated with cardiovascular instability, particularly hypotension or hypertension, in patients with marginal cardiac reserve. The data do not suggest an obvious mechanism(s) except that dose or infusion rate of ALF, premedication with atropine and pretreatment with pancuronium are not causes of or protectors against cardiovascular instability. While diazepam premedication lowers SBP throughout the induction-intubation sequence, it is not otherwise an explanation for cardiovascular instability. Our findings indicate that patients > 60 yrs of age and those receiving slower infusions or having diazepam premedications require less ALF for induction of anesthesia. The data confirm that induction of anesthesia with ALF may be associated with more cardiovascular instability than was previously recognized in patients with limited cardiovascular function but do not indicate an obvious reason for this finding.

Table 1: Systolic Blood Pressure During the Induction-Intubation Sequence (mmHG; Mean + SEM)

	Baseline	Minimum	Maximun
All Subjects n = 160	150 ± 2.1	118 ± 2.3	162 ± 2.4
No Diazepam n = 79	154 ± 3.1	125 ± 3.4	169 ± 3.3
Diazepam n = 81	146 ± 3.1*	112 ± 2.0*	155 ± 3.2*

*$p < 0.05$ when compared to no diazepam.

Table 2: Heart Rate During Induction (bpm; Mean + SEM)

	Baseline	Minimum	Maximum
All Subjects n = 160	77 ± 1.4	73 ± 1.5	93 ± 1.7
No Diazepam n = 79	79 ± 1.9	77 ± 2.2	97 ± 2.4
Diazepam n = 81	74 ± 2.0	70 ± 1.9	88 ± 2.2

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Title: EPIDURAL BLOOD PATCH: DIRECTION OF THE NEEDLE BEVEL AND SPREAD OF BLOOD INJECTED INTO THE EPIDURAL SPACE

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Introduction. Many factors have been invoked as determinants of the spread of solutions in the epidural space, some of which are of demonstrable clinical importance in determining the extent of spread into the epidural space. Although often mentioned, other factors such as the direction of the epidural needle bevel are considered hypothetical (1,2,3). The objective of this study is to evaluate the influence of the direction of the epidural needle bevel on the spread of blood into the epidural space during an epidural blood patch (EBP).

Methods. The study was approved by the Committee for Human Research of our institution. Informed consents were obtained from all the patients prior to their entry into the study. A total of 9 (ASA I & II) patients with post lumbar puncture headache, agreed to the procedure after conservative treatment had failed for at least 48 hours. The study group included seven females and two males. Their ages ranged from 18 to 51 years. Three patients had postural headache after spinal anesthesia; one in whom a 22 gauge needle was used, the other two a 25 gauge needle. Six patients had inadvertent dural puncture during the initiation of epidural anesthesia with a 17 gauge Touhy needle. After the placement of the blood pressure cuff and EKG, a 16 gauge I.V. catheter was inserted using sterile technique in a large vein in the antecubital fossa. Stannous chloride 2.5 mg was injected I.V., to prelabel the RBC's. Half an hour later the patient was placed in the lateral decubitus position, prepped and draped. The interspace of the previous dural puncture was identified and a 17 gauge Touhy needle was used to enter the epidural space. Using sterile technique, an assistant aspirated 10 ml. of autologous blood, from the I.V. site, into a syringe containing 2 to 4 millicuries of Technetium 99M pertechnetate and mixed them gently for two minutes. The labeled RBC's were then reinjected into the epidural space at the rate of one ml. per 3 seconds. The 9 patients were equally divided into 3 groups. In the first group the blood was injected with the bevel of the needle pointing cephalad. In the second group the bevel was pointing caudad. In the third group 8 ml. of blood was injected with the bevel of the needle cephalad; the needle was then rotated 180° and the rest was injected caudad. After the 10 ml. of labeled blood were injected, additional amounts of non-labeled blood was injected until the patient reported discomfort or pain in the back, buttocks or legs. All the patients were studied by imaging techniques using a gamma camera with a parallel hole collimator. Dynamic images were obtained every 3 seconds during the injection of blood. In addition, delayed posterior and lateral views were taken in most of the cases thirty minutes and three hours following the injection.

Results. The dynamic images during the injection into the epidural space showed spread of blood in all directions away from the point of the needle. The blood injected into the posterior epidural space followed three routes of dispersion. First a longitudinal spread along the cranio-caudal axis, then circumferentially around the dura to the anterior epidural space and finally laterally through the intervertebral foramina into the paravertebral space. The blood into the epidural space tended to travel more easily upward in a cranial direction than downward towards the caudal canal. Even with the bevel of the needle pointing caudad the blood spread cephalad, with little tendency to caudad distribuution as has been postulated. In most cases, the films revealed that the caudad spread of blood stopped at the level of S_1 or upper part of S_2. The cephalad spread instead showed a considerable range between T_5 and L_1. The volume of blood injected varied between 12 and 18 ml. with a mean volume of 14.5 ml. The extent of the spread of blood in the epidural space varied between 7 and 14 segments, with a mean of 9 segments. The mean spread of blood was 6 segments upwards and 3 segments downwards. No complication was reported at the time of the EBP or at 3 months follow up.

Discussion. It may seem self evident that the direction of the needle bevel should play a role in the physical spread of solutions within the epidural space. Some authors sustain this concept (1,2,3). However, in our study, the results indicate that the direction of the bevel of the epidural needle has no influence on the spread of blood into the epidural space. Usubiaga (1) and Moore (4) using radiological techniques studied the spread of radiopaque solutions injected into the epidural space. Our study using radioactive material supports their findings; in addition, it shows that the cephalad spread will occur regardless of the orientation of the needle bevel. It is reasonable to assume that success of the EBP depends upon a close approximation of the injected blood to the puncture site. For this reason, injection at the same interspace is advisable but not mandatory. If for any reason that interspace cannot be used, one below would be more appropriate because of the easier cephalad spread of blood in the epidural space.

In conclusion, the direction of the needle bevel is of no significance in the spread of blood and probably of local anesthetic solutions in the epidural space.

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Title: SUFENTANIL FOR ANALGESIA AFTER CESAREAN SECTION: INTRAVENOUS VERSUS EPIDURAL ADMINISTRATION

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Introduction. Administration of epidural morphine has become widespread in the management of postoperative pain. However, the risk of late respiratory depression from cephalad spread of the opioid in the CSF remains a disadvantage for low risk patients who are not closely monitored. The rapidly acting, highly lipid soluble opioid analgesic sufentanil is more likely to remain localized within neural tissue and may pose less of a hazard in this respect. The aim of this study was to compare serum sufentanil levels following intravenous and epidural administration, and to make preliminary evaluations of the efficacy and safety of this agent in the management of pain following cesarean section. In addition, we examined the effect of epinephrine on serum sufentanil levels and the duration of analgesia following epidural sufentanil.

Methods. The study was approved by the Human Subjects Committee and informed consent obtained from 16 parturients undergoing cesarean section under epidural anesthesia. Surgical anesthesia was provided with lidocaine 2% with 1:200,000 epinephrine. Ten minutes after delivery, patients received either epidural sufentanil, 50 ug (Group I, n=6); epidural sufentanil, 50 ug, with 1:200,000 epinephrine (Group II, n=5); or intravenous sufentanil 25-50 ug (Group III, n=5). Although the intention was to administer the same dose intravenously as epidurally, only one patient tolerated this dose without becoming excessively sedated or hypotensive. One subject received 40 ug, two 30 ug, and one only 25 ug i.v. Venous blood was collected at 5-10 min intervals for 1 h, 15 min intervals for the next hour, and subsequently every 30-60 min for up to 4 h after injection. Serum sufentanil levels were measured using a radioimmunoassay technique. The duration of analgesia (time until the patient requested additional analgesics) and the presence of side effects were recorded. Data were analyzed using ANOVA and chi-square analyses with P<0.05 regarded as statistically significant.

Results. The groups were similar with respect to age, height, and weight. Group III patients received sufentanil 35±10 mg (mean ± S.D.) intravenously over 5-10 min. Serum levels of sufentanil for all groups are shown in Fig. 1. Peak sufentanil levels occurred in less than 30 min following epidural sufentanil, plain; between 60 and 90 min when epinephrine was added; and within 10 min following i.v. sufentanil. Duration of analgesia was 219±118 min in Group I, 258±36 min in Group II, and 101±47 min in Group III (P<0.05, Groups I and II vs. Group III). Serum sufentanil levels >0.2 ng/ml were required for postoperative analgesia following i.v. administration, whereas analgesia persisted following epidural administration in spite of low serum sufentanil levels (<0.1 ng/ml). The incidence of common side effects did not differ significantly among the groups and is summarized in Table 1.

Discussion. Even though larger doses of sufentanil were injected epidurally than intravenously, serum drug levels were consistently lower following epidural administration. These data support the hypothesis that the more prolonged analgesia obtained with epidural sufentanil is due to a spinal, rather than a systemic effect. Epinephrine appeared to delay the peak in serum sufentanil levels following epidural administration. Although the duration of analgesia tended to be prolonged by the addition of epinephrine, these data are inconclusive because of the small number of patients in each group.

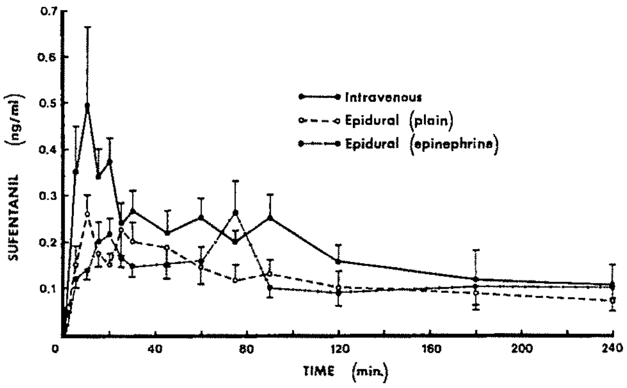

Figure 1. Serum sufentanil levels following either intravenous or epidural administration (mean values ± S.D.)

Table 1. Side Effects

	Group I (n=6)	Group II (n=5)	Group III (n=5)
Sedation	5	2	4
Hypotension	0	0	1
Nausea	3	1	3
Vomiting	0	1	2
Pruritis	2	3	2
Resp. depression	0	0	0

Title: HALOTHANE IS A POTENT MYOCARDIAL DEPRESSANT DURING FENTANYL-ANESTHESIA

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Introduction Few investigators have analyzed the effects of halothane on myocardial function in man (1). The reported studies have usually been performed on healthy volunteers or ASA I patients and have demonstrated moderate reductions (10-15%) in ventricular performance at 1% end-tidal halothane. Interpretation of the performance data has been complicated by the use of contractility indices which are known to be affected by ventricular loading conditions. Recently Sagawa has introduced the end-systolic pressure-volume relation (ESPVR), a new index of contractility which is independent of loading conditions (2). The aim of this study was to assess the effects of halothane on the ESPVR in patients with ischemic heart disease, undergoing coronary bypass surgery (CABG).

Methods Informed consent was obtained from ten CABG patients. In all patients anesthesia was induced with fentanyl, pancuronium, and 100 % O_2, and maintained with fentanyl (total dose: 100±15 mcg/kg). The ESPVR measurements were obtained immediately before or after cardiopulmonary bypass (CPB). Continuous recordings of the radial artery pressure and of the left-ventricular short-axis area, obtained by epicardial placement of a 3.5 mHz ATL® transducer, were synchronized. During the recording, 200-300cc of pump-fluid were rapidly transfused into the right atrium. The recordings were then interrupted and halothane was administered until a stable end-tidal concentration of 1% was achieved. A second transfusion was delivered while pressure and 2D-echo data were again recorded. With the information from each transfusion, an ESPVR-slope was constructed using 6 separate cardiac cycles. Peak-systolic pressure was defined as end-systolic pressure, while end-systolic volume index was derived from the smallest short-axis area for the studied heartbeat. All echo-data were analyzed by a "blinded" investigator using a Diasonics® interactive computer. Student's T-test was used to assess statistical significance.

Results Seven patients were studied immediately before bypass, the remaining three patients after CPB. At control the mean contractility as expressed by ESPVR was 1.45±0.80 mmHg/ml/m^2 (±SD). Administration of 1% end-tidal halothane resulted in a 52% reduction of the contractility-slopes to a mean value of 0.70±0.55 mmHg/ml/m^2 (±SD). The difference was statistically significant ($p<0.02$) (Figure). The x-axis intercept (V_0), an index of afterload, was -48.88±97.26 ml/m^2 (mean±SD) at control, and was -147.45±190.63 ml/m^2 (mean±SD) after halothane administration. The difference was not statistically significant.

Discussion Before the administration of halothane, the contractility of the studied patients was not significantly different from that measured in a larger group of patients by these investigators under similar circumstances. After 1% end-tidal halothane, the myocardial depression was of greater magnitude than in any previous human study. Another study in which the effects of halothane were investigated by means of the end-systolic pressure-dimension, was published by Van Trigt et al (3). They implanted ultrasonic microcrystals in 7 patients undergoing myocardial revascularization and after CPB they observed a 29% reduction in end-systolic pressure-dimension slopes at 0.5% end-tidal halothane. It thus appears that the ESPVR is a more sensitive index of contractility than the traditional indices. The patients in this study all presented with ischemic heart disease and were undergoing coronary artery surgery. It is possible that they were more sensitive to the effects of the drug than healthy volunteers or that fentanyl interfered with protective compensatory mechanisms. In most published reports, halothane does not affect afterload expressed as systemic vascular resistance, and our findings tend to support this.

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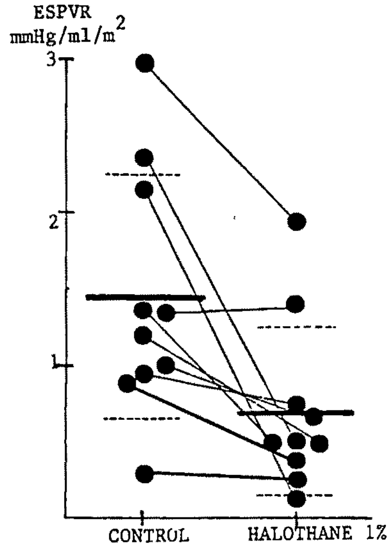

Title: THE PRIMING EFFECT OF VECURONIUM IN CHILDREN

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Introduction. The administration of a small dose of muscle relaxant preceding the clinical dose of said muscle relaxant has been shown to hasten the onset of the muscle relaxation — so called the priming principle as advocated by Foldes and others.[1] Vecuronium, a new non-depolarizing muscle relaxant of intermediate duration has an average onset of 2.4 min. in children[2], which is faster than that of pancuronium or curarine but still slower than that of succinylcholine. The present study was undertaken to evaluate the priming effect of vecuronium in pediatric patients.

Method. This study was approved by the institutional Review Board and informed consents were obtained from parents of all the patients prior to their entry into the study. Thirty ASA Class I-II children, age ranging from 1-12 years, undergoing elective surgeries were premedicated with atropine 0.01 mg/kg IM and anesthetized with halothane in nitrous oxide and oxygen (2:1) by mask. After attaining a stable plane of anesthesia at 1.5% halothane, patients were divided randomly into two equal groups with group A of 15 patients receiving a single injection of 65 mcg/kg vecuronium IV and group B of 15 patients receiving a priming dose of 15 mcg/kg vecuronium IV followed by a second dose of 50 mcg/kg 6 minutes later. The neuromuscular block was monitored continuously in all patients with Datex Relaxograph EMG monitor which recorded the twitch response of the thumb adductor to ulnar nerve stimulation with supramaximal Train-of-Four stimuli at 2 Hz. Endotracheal intubation was performed when twitch height reduced to 90% depression and the intubating condition was rated by a four point scale of excellent, good, poor, not possible. After intubation, anesthesia was maintained by halothane 1% in N_2O and O_2 (2:1 ratio). Ventilation was controlled to keep end-tidal Pco_2 at 30-40 mmHg and rectal temperature was maintained at 35-37°c. Clinical duration of muscle relaxant was measured as the time from injection to spontaneous recovery of twitch to 25% of control.

Results. Both groups were comparable in their demographics with age distribution of 6.2 ± 4.0 years for group A and 6.1 ± 3.0 for group B (Table I). There was no significant difference between the two groups in either the maximal degree of twitch depression or spontaneous recovery time. However, the onset for 90% twitch depression was much shorter for group B, being 1.5 ± 0.5 minutes, than that for group A (2.6 ± 0.8 minutes), and the difference is statistically significant with $P < 0.001$. Conditions for endotracheal intubation were rated excellent in 13/15 and good in 2/15 patients in group A, and excellent in 12/15 and good in 3/15 patients in group B (Table II).

Discussion. Vecuronium offers the advantage of shorter duration of action and lack of cardiovascular effects when compared with the older non-depolarizing muscle relaxants, namely pancuronium, d-tubocurarine and metocurine and its use in children has been reported to have great safety.[3] When administered intravenously in two divided doses, 15 mcg/kg followed by 50 mcg/kg, vecuronium provided equally satisfactory conditions for tracheal intubation with a much faster onset compared to that of single bolus dose of 65 mcg/kg. Such a priming effect as demonstrated in our study in pediatric patients is in accordance with that reported by Foldes, et al. using the same regiment in adult patients.[4] The more rapid onset time by using a priming dose makes vecuronium closer to the ideal muscle relaxant for clinical use.

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TABLE I: DEMOGRAPHIC DATA

GROUP	A (n=15)	B (n=15)
AGE	6.2 ± 4.0 yrs	6.1 ± 3.0 yrs
SEX	7 M, 8 F	8 M, 7 F
WEIGHT	15.7 ± 6.2 kg	17.1 ± 4.3 kg

TABLE II: NEUROMUSCULAR EFFECT OF VECURONIUM

GROUP	A (n=15)	B (n=15)
Dose	65 mcg/kg bolus	15 mcg/kg First 50 mcg/kg 6 min. later
Maximal twitch depression	93.3 ± 3.2%	97.7 ± 2.0%
Onset time for 90% twitch depression	2.6 ± 0.8 min.	1.5 ± 0.5 min.*
Time from injec. to 25% spont. recovery	26.1 ± 7.7 min.	23.6 ± 8.1 min.
Intubating condition	Excellent: 13/15 Good: 2/15	Excellent: 12/15 Good: 3/15

*$p < 0.001$

Title: COMPUTERIZED INFUSION OF SUFENTANIL: A COMPARISON OF MORBIDLY OBESE AND NONOBESE PATIENTS

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Introduction: The use of an exponential infusion rate to maintain a predictable therapeutic plasma level of narcotic has been demonstrated (1). Our purpose was to:

a. Test whether narcotic exponential infusions were feasible to maintain clinical anesthesia in obese vs nonobese patients.
b. Evaluate the administration of drug based on ideal body weight (IBW) in two populations of significantly different weights.

Methods: After obtaining informed consent, two groups of patients were studied: Mean values are expressed with their standard deviation. Group O, 10 patients (females, age 29 ± 5 years with actual body weight (ABW) 123 ± 20 kg) underwent upper abdominal surgery (gastroplasty); Group N, 10 patients (6 females and 4 males, age 41 ± 15 years (p=0.03) with ABW 80 ± 17 kg, p=0.001) underwent upper abdominal surgery (cholecystectomy, bowel resection or staging laparotomy). Ideal body weight (IBW) for Group O and N were not significantly different.

All patients were premedicated with 10 mg of diazepam orally. An exponential programmed IMED 929 pump infused sufentanil (concentration 1 mg$\cdot$ml^{-1} D5W) to achieve a constant blood level. The theoretical level was calculated for IBW (Metropolitan Insurance Company Tables 1983) and set at 1 ng$\cdot$ml^{-1} plasma concentration. The induction sequence was standardized for all patients as follows:

0 minutes:	Infusion started and d-tubocurare 3 mg, injected.
3 minutes:	Thiopental sodium, 3-4 mg$\cdot$kg^{-1} of IBW, injected.
3.5 minutes:	Succinylcholine, 100 mg, given.
5 minutes:	Laryngoscopy for 30 seconds and intubation were performed.

Anesthesia was maintained with nitrous oxide and oxygen (F_iO_2 = 0.4). Muscle relaxation was achieved with atracurium as required. Diazepam, 2 mg, was given after intubation and repeated at 30 minute intervals until isoflurane had been introduced. Sufentanil infusion was terminated after 45 minutes and replaced with isoflurane (0.25% - 1% inspired) to prevent an increase in blood pressure and/or heart rate above 30% of baseline levels.

Blood pressure was measured with a dinamap (Critikon) and directly via radial arterial catheter. EKG was observed on datascope, end-expired CO_2 (Puritan-Bennett) was maintained between 35 and 42 mm Hg and correlated with arterial blood gas values.

Arterial blood samples for sufentanil levels were drawn prior to infusion and at minutes 5, 10, 15, 30, 45, 50, 55, 60, 75, 90, 120, 150 after the infusion was started. Samples were also taken at anesthesia induction, skin incision, and extubation. Analysis of sufentanil levels was done by radioimmunoassay at Janssen Pharmaceutica (2), sensitivity of assay of 0.1 ng$\cdot$ml^{-1}.

Results: The mean ABW for the O patients exceeded IBW by 86%, whereas the ABW for Group N was only 23% greater than IBW (p=0.0001). Values of heart rate and blood pressure were maintained within 30% of baseline levels. The duration of surgery for Group N patients 218 ± 59 minutes vs 127 ± 26 minutes for Group O patients (p=0.0003). Time of extubation (from discontinuation of nitrous oxide) for Group N 17 ± 8 minutes vs 16 ± 16 minutes for Group O patients. There was no need to change the infusion rate nor make any pharmacological interventions to stabilize the hemodynamic parameters. Note, all patients had incision and abdominal exploration within 45 minutes, i.e. prior to commencing isoflurane.

Sufentanil Plasma Levels

The mean total sufentanil administered to Group O was 115 ± 11.5 μg (0.96 ± 0.20 μg$\cdot$kg^{-1} of ABW), and 116 ± 13.0 μg (1.50 ± 0.34 μg$\cdot$kg^{-1} of ABW) given to Group N patients. The actual plasma levels of sufentanil for both groups showed marked interindividual variations. However, the levels were consistent within individuals and mean levels were comparable in both groups: 1.29 ± 0.41 ng$\cdot$ml^{-1} (range 0.78-1.88 ng$\cdot$ml^{-1}) for Group O and 1.41 ± 0.31 ng$\cdot$ml^{-1} (0.76-1.80 ng$\cdot$ml^{-1}) for Group N. The dosing rate had been calculated to produce a plasma level of 1 ng$\cdot$ml^{-1} in patients of IBW. The measured levels in the much heavier patients were greater instead of less as would be predicted. Zero incidence of recall was noted. The actual concentrations of sufentanil showed a 2- to 3-fold variations in both groups. However, all concentrations were clinically effective in attenuating hemodynamic responses to stimuli.

Discussion and Conclusion: This study has demonstrated:

1. Sufentanil levels were similar in both groups (see figure). The expected greater redistribution into fat was not evident from the plasma levels probably because of the steady state achieved by the infusion.
2. Correct dosage is better correlated with IBW than ABW.
3. An exponential infusion of a potent narcotic with N_2O + O_2 provides acceptable anesthetic conditions for major upper abdominal surgery.

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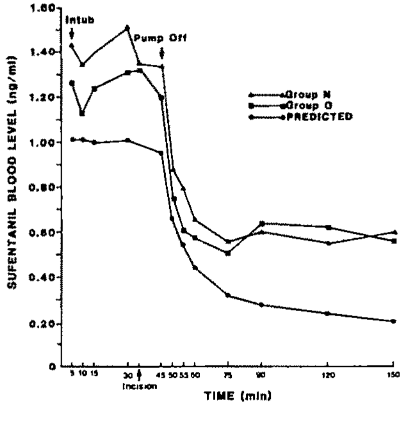
SUFENTANIL LEVELS IN MORBIDLY OBESE AND NON OBESE PATIENTS

Title: **RANDOMIZED EVALUATION OF INDUCTION AND RECOVERY FROM ANESTHESIA WITH DIPRIVAN OR THIOPENTAL SODIUM**

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Introduction. Diprivan (formerly disoprofol, 2.6 disopropylphenol, ICI 35.868 Propofol) is one of a series of alkylphenols which has anesthetic properties. Initial investigations with insoluble diprivan used a surfactant Cremophor EL as a vehicle and demonstrated rapid induction of anesthesia and short duration of action. Due to associated anaphylactoid reactions and painful injection with Cremophor containing agents, an emulsion formulation of 'diprivan' was developed. We compared the induction and recovery characteristics of equipotent doses (ED95) of diprivan 2.5 mg/kg[1] and thiopental 4 mg/kg. Since $t\frac{1}{2}\ \alpha$ of diprivan is + 2.5 min and $t\frac{1}{2}\ \beta$ 55 min, we expected a rapid induction and a quick recovery.

Methods. Forty ASA I and II, 18-65 year old informed and consenting patients, scheduled for short elective gynecological procedures were invited to participate in this study which was approved by the Institutional Review Board. Patients were excluded if they were obese (> 30% of Metropolitan Insurance ideal body weight), had significant hepatic, renal, cardiac or respiratory disease, or had a history of allergy to the test drug or its constituents. Premedication was standardized for all patients and consisted of Flurazepam 15 mg night before, diazepam 10 mg po on call to surgery and sufentanil 12.5 μg iv 5 min prior to induction. Anesthesia was randomly induced with either 2.5 mg/kg of diprivan or 4 mg/kg of thiopental over 20 sec in a freely running iv infusion of D_5RL (compatability tested at ICI) in the dorsum of the hand. Induction time was ascertained from the end of injection when patients ceased repetitive hand squeezing and lost their eyelid reflex.

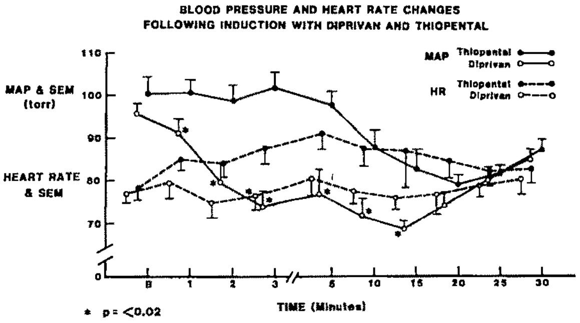
A post induction observation time of 3 min (during which patients received only O_2 and ventilatory assistance if needed) was used to observe induction characteristics, including excitement, movement, twitching, color changes or inadequate anesthesia. Awake patients were allowed up to 2 supplementary doses of 25% of the induction dose at 1 min intervals. Three min after the induction, patients were given 1 mg/kg of succinylcholine and intubated. Anesthesia was maintained with 60% N_2O:40% O_2 and isoflurane if needed to keep hemodynamic parameters within 20% of baseline. Atracurium was used to achieve muscle relaxation (if required). There were no significant differences in the two groups for age, sex, race, height or body weight.

Results. All 40 patients were induced smoothly and quickly in a mean induction time of 34 sec for diprivan and 43 sec for thiopental (NS). One patient in each group required a supplementary dose to maintain anesthesia for 3 min. Intravenous irritation occurred in 2 diprivan patients, who reported tingling and hot feeling; respectively. Nobody complained of pain in either group. Movement was associated with light anesthesia in 2 patients (1 in each group). Involuntary movement or excitement did not occur. Hiccups occurred with 1 diprivan patient (5%) and 2 thiopental patients (10%). Atracurium was used equally in both groups. Diprivan patients had significantly lower systolic and diastolic pressures and lower heart rates than patients receiving thiopental for 15 minutes after induction. Thereafter, the differences were not significant. Parr scores in the recovery room for diprivan and thiopental patients were not significantly different.

Discussion. The overall quality of induction was good in 95% of patients. Five percent (1 in each group) had spontaneous movements, probably reflecting light anesthesia. The dose of 2.5 mg/kg for diprivan given shortly after an acute narcotic premedication proved ample for induction. All patients were apneic for a variable period after bolus of induction agent. The airway was easily maintained and ventilation was supported throughout the 3 min observation period. Following diprivan induction, laryngoscopy produced mild increases in blood pressure and heart rate. This may be protective in patients with compromised cardiovascular function. The recovery phase with diprivan was remarkable for lack of excitement or emetic sequelae. Recovery from both drugs was affected by the addition of a volatile agent for variable periods. The diprivan patients tended to awaken (calculated from discontinuation of N_2O) quicker at 7 min vs 10 min for thiopental. The difference was not significant. Diprivan was shown to be a safe and efficacious induction agent with a rapid onset and quick recovery. Rapid onset is a desirable feature allowing the dose to be titrated. Rapid elimination suggests the use of this drug for infusion.

Table 1 **Induction and Recovery Times of Diprivan and Thiopental**
(Mean + SD)

	Induction Time (sec)	Duration Time (min)	Awake Time (min)	Orientation Time (min)
Diprivan	34+11	38+24	7+6	10+6
Range	19-64	15-105	1-25	2-28
Thiopental	41+11	45+23	10+7	14+11
Range	13-70	20-110	3-29	4-45



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Title: EXPERIENCE WITH LUMBAR EPIDURAL HYDROMORPHONE FOR PAIN RELIEF AFTER THORACOTOMY

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Introduction. Narcotics administered via the lumbar epidural route have been shown to be beneficial in providing pain relief and preserving pulmonary function in patients undergoing thoracotomy.[1,2] The administration of hydromorphone (Dilaudid®) for epidural analgesia has not been reported previously.[2] Hydromorphone has several properties that recommend its use for epidural administration.

Methods. The charts of 21 patients who underwent thoracotomy during 1983 and who received epidural hydromorphone were reviewed. Hydromorphone was selected for epidural administration because the commercially available preparation is preservative free. All patients had a lumbar epidural catheter placed in their L_{2-3} interspace prior to induction of general anesthesia. Correct placement of the epidural catheter was confirmed with lidocaine (1.5%), 10-15 ml with epinephrine 1:200,000 after a sensory block was achieved. Narcotics were not given as a premedication. Two of the 21 patients (9.5%) received fentanyl on induction of anesthesia. No other patients received narcotics intraoperatively. All patients were given 1.25-1.5 mg of hydromorphone epidurally in 10-15 ml of normal saline approximately 45 minutes before the completion of surgery. Subsequent doses of epidural hydromorphone were given when necessary as long as the patients remained in the intensive care unit (ICU). The duration of action of epidural hydromorphone, and the amounts of any supplemental intravenous morphine administered were recorded. Side-effects associated with epidural narcotics (respiratory depression, pruritus, and nausea and vomiting) were noted when they occurred. All patients had indwelling urinary catheters so the incidence of urinary retention with epidural hydromorphone in our series could not be determined.

Results. The mean age of the patients was 58.5 years (range of 18-76 years). Five patients initially received 1.25 mg of epidural hydromorphone and 16 patients received 1.5 mg of hydromorphone. Second doses varied from 1.25 mg to 2.0 mg. The mean duration of analgesia after the initial dose of hydromorphone was 7.7 ± .9 hours (range being 3-18 hours). The mean ICU stay was 32.5 hours with a range of 19-70 hours. The amount of intravenous morphine required to supplement the epidural hydromorphone for analgesia while the patient was in the intensive care unit was 4.4 ± 1.7 mg. Three patients (14.3%) had a $PaCO_2 > 55$ mmHg and were treated with i.v. naloxone. Two of these 3 patients had been given an epidural dose of 2.0 mg of hydromorphone prior to their documented hypoventilation. No patient in our series had a respiratory rate less than 8/min. Only one patient (4.8%) complained of pruritus which was not generalized but localized to the area around his oxygen mask. Two patients (9.5%) experienced nausea and vomiting.

Discussion. One advantage of epidural administered hydromorphone is that hydromorphone releases less histamine than morphine and thus may be associated with a lower incidence of pruritis. Only 1 patient in our series complained of pruritus, a very common complication of epidural morphine.[2] Since hydromorphone is slightly more lipid soluble than morphine, it may produce a segmental analgesic pattern with less rostral spread and presumably a lower incidence of respiratory depression than with epidural morphine.[3] There were 3 cases of alveolar hypoventilation ($PaCO_2 > 55$ mmHg) in our series of 21 patients. Since 2 of these 3 patients received a large dose of hydromorphone (2.0 mg), this complication may have been dose related. Hydromorphone is available as a preservative free preparation and is much less expensive than commercially prepared preservative free morphine. The duration of action of epidural hydromorphone is reasonably long and it provides excellent analgesia in patients undergoing thoracotomies. Only a few patients required small amounts of parenteral narcotics to supplement the analgesia obtained by epidural hydromorphone. In our clinical experience, 1.25-1.5 mg of hydromorphone in 10-15 ml of saline administered via a lumbar epidural catheter provided excellent post-thoracotomy pain relief with fewer side-effects than have been reported after epidural morphine.

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Title: EPIDURAL TEMPERATURE: A CAUSE OF SHIVERING DURING EPIDURAL ANESTHESIA

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Introduction. Shivering is a recognised complication of epidural anesthesia (1). Various causes of such shivering have been suggested: namely (a) a decrease in core temperature due to peripheral vasodilation caused by sympathetic blockade, (b) an effect of local anesthetic after absorption into the circulation, (c) a differential inhibition of afferent thermoreceptor fibers within the spinal cord causing an erroneous indication of a fall in peripheral temperature (2), and (d) a direct effect of cold anesthetic solution upon thermosensitive structures within the spinal cord. There is little evidence that (a), (b), or (c) are important to such shivering (3). On the other hand, there is abundant evidence that thermosensitive structures exist within the spinal cord of various mammalian species (4), and recent research suggests that shivering can be activated by local cooling of the spinal canal in man (5). The aims of the present study were to: (i) determine the incidence of shivering when 0.5% bupivacaine at 4°C is injected into the epidural space; (ii) record the temperature changes within the epidural space caused by these injections; (iii) learn if shivering can be reversed by injection of warm local anesthetic.

Methods. Following approval by the Institutional Review Board, 30 patients (mean age 27.2, ± SEM 0.82) who were scheduled for postpartum tubal ligation under epidural anesthesia gave informed consent to participate in the study. No patients were febrile or were receiving medications preoperatively. One liter of Ringer's lactate solution warmed to 37°C was given i.v. before the epidural needle was inserted. An 18g Concorde epidural catheter with a thermistor probe (Yellow Springs Instruments #511) threaded to its tip was inserted into the epidural space. A dose of 4 ml 0.5% bupivacaine cooled to 4°C was injected through the catheter followed by doses of 7 and 5 ml at the same temperature. If shivering had not occurred by the third dose, a further cold injection was given. In certain shivering patients bupivacaine warmed to 41°C was given in an attempt to reverse the shivering response. Air temperature, core temperature, and average skin temperature (6) were monitored. Shivering was recorded by electromyography with sensors placed over the anterior shoulder girdle muscles. Once a block to a T_6 sensory level was reached, the study was terminated.

Results. The mean weight of the patients was 65.3 kg (SEM ± 2.85), and the mean total dose of bupivacaine used was 21.9 ml (SEM ± 0.64). 14 of the 30 patients (47%) shivered after 1 or more cold injections. Injections of cold anesthetic caused epidural temperatures to decrease to below 20°C and to remain below 37°C for several minutes. When shivering occurred, it began within 3.5 to 4.4 minutes after injection (Table 1).

Table 1.

	Dose 1 (4 ml)	Dose 2 (7 ml)	Dose 3 (5 ml)	Dose 4 (5 ml)
Mean time from injection to return to 37°C (mins ± SEM)	7.36 ± 0.43 n=30	13.3 ± 0.51 n=30	11.0 ± 0.49 n=30	11.1 ± 0.50 n=19
Mean time from injection to start of shivering (mins ± SEM)	---	3.46 ± 2.05 n=5	4.36 ± 0.52 n=5	4.2 ± 0.79 n=7

In eight of the 14 patients shivering was marked and in 4 of these patients it was reduced or stopped by an injection of 0.5% bupivaine warmed to 41°C. There were no significant differences in ambient, core, or mean skin temperatures for shivering versus nonshivering patients.

Discussion. The initiation of shivering depends on the interaction of three factors: input from peripheral cold receptors, input from non-hypothalamic thermosensitive neurons (e.g. spinal cord) and the temperature of the hypothalamus. In this study neither core temperature nor cutaneous temperature were affected. Hence these findings provide evidence for the presence of thermosensitive tissue within the spinal canal of man. These results suggest that shivering during epidural anesthesia is very common, that anesthetics kept at refrigerator temperatures can cause marked and prolonged decreases in the temperature of the epidural space and that warming of the anesthetic may prevent shivering.

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Title: COMPARISON OF ISOFORANE VS. FENTANYL ANESTHESIA IN LIGATION OF THE PATENT DUCTUS ARTERIOSUS IN PRETERM INFANTS

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Introduction. The increasing number of prematurely born infants of low birth weight who are surviving in neonatal intensive care units present many problems. Patent ductus arteriosus (PDA) is one of the most frequently occurring problems, occurring in as many as 90% of infants of 1500 gm or less.[1] Anesthetic agents given during ligation of the PDA may be used to control the pressure gradient from the aorta to the pulmonary artery. Both inhalational agents, Halothane[2] and high dose Fentanyl[3], have been used successfully for PDA ligation. In some institutions no anesthetics are used.[4] The purpose of this study was to evaluate the effectiveness of an inhalational anesthetic agent, Isoforane, versus Fentanyl (50mcg/kg) anesthesia with respect to the stability of heart rate, blood pressure, and the oxygen saturation of the arterial blood.

Methods. Ten premature infants between 26-32 weeks gestation were studied who needed ligation of PDA for clinically significant left to right shunt as evidenced by respiratory distress syndrome, failure to wean, congestive heart failure, and LA/AO ratio >1. All were less than 2 kg. in weight and had failed medical management. Patients were assigned to either of two groups: Group A- Forane-Pavulon anesthetic; or Group B- Fentanyl-Pavulon anesthetic. Group A- Patients received Isoforane anesthesia (.25 to 1.0%) in air-oxygen misture with oxygen concentration sufficient to maintain an arterial oxygen saturation 85%.

Group B- Patients received Fentanyl 50 mcg/kg prior to incision. They were ventilated with an air-oxygen mixture as above. Mean arterial blood pressure (MAP), heart rate (HR), and oxygen saturation (SaO_2) were compared between group A and B at six stages of the operation: 1-Prior to induction, 2-At induction, 3-Chest incision, 4-Lung retraction, 5-Ligation of PDA, 6-After chest closure. All patients were paralyzed with .2 mg/kg Pavulon and received a 10 ml/kg bolus of D_5LR prior to induction. All were monitored with a Nellcor pulse oximeter and pediatric Dinamap. Protocol approved by the Human Subjects Research Committee, and consents were obtained.

Results. Both groups were clinically judged to have satisfactory anesthesia. Average weight in the Fentanyl group was 1084 gm, and 1032 gm in the Isoforane group. The Fentanyl group, from the start, had a consistently higher MAP ($P < 0.05$) compared to the Isoforane group, with higher MAP increases during surgical manipulation (See figure). Heart rate was not significantly different between the two groups at any stage, with both groups showing a stable course without significant changes during the operation (See table). Oxygen Saturation decreased to low levels (<85%) in the Fentanyl group during lung retraction (Stage 4) only and was otherwise stable in both groups (See table). However, there were no changes in SaO_2 of statistical significance between the two groups.

Discussion. Robinson and Gregory[3] found that administration of Fentanyl bolus was associated with a 5% decrease in systolic blood pressure. They reported[2] that post induction blood pressure with Halothane anesthetic decreased more than 30% in 46% of their patient population. However, the Fentanyl group had received a 10ml/kg bolus of Lactated Ringers solution with 5% Dextrose intravenously prior to induction. Isoforane is metabolized far less than Halothane and may be safer to use in the infant. It also has a stronger depressant effect on the SVR and may produce less myocardial depression, which may be useful in controlling the pressure gradient from the aorta to the pulmonary artery. In this study, both high dose Fentanyl and Isoforane produced a stable heart rate and oxygen saturation. Both allowed high concentrations of oxygen to be used during the lung retraction The Fentanyl group had higher MAP fluctuations during surgical manipulations.

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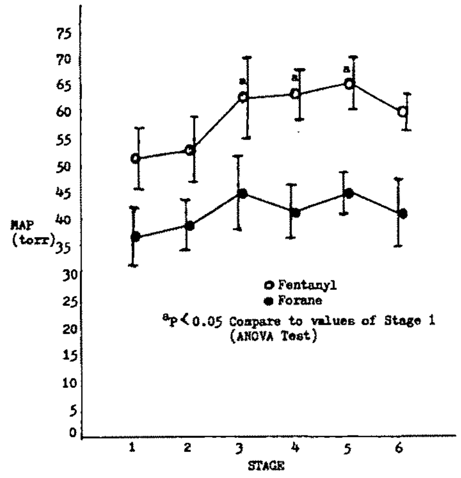
TABLE I

	Stage**	1	2	3	4	5	6
MAP(torr)	Forane	38±5.7	39±4.2	45±7.4	42±4.8	45±3.8	41±5.5
M+SEM	Fentanyl	*52±5.9	*53±6.3	*63±7.6	*64±4.7	*65±4.4	*60±2.8
HR(BPM)	Forane	176±8.2	174±7.5	176±11	174±8.4	172±9.7	175±11
	Fentanyl	165±9.6	168±11	165±9.4	163±8.8	169±7.8	174±8.0
SaO_2(%)	Forane	96±1.3	96±0.5	92±2.8	90±3.1	91±2.7	94±1.1
	Fentanyl	88±2.4	91±2.3	89±2.7	83±5.3	96±1.4	95±1.9

*$P < 0.05$ compare to values of Forane group at corresponding stage. (Non paired t test)
**See Methods



THE CARDIOVASCULAR EFFECTS OF PROPOFOL IN PATIENTS WITH IMPAIRED CARDIAC FUNCTION

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Propofol (Diprivan), an ultra-short acting non-barbiturate anesthetic induction agent is being proposed as an alternative to etomidate and thiopental because of its rapid onset of action (45-60 seconds), short duration (3-5 minutes), clear-headed recovery and apparent absence of significant cardiovascular side-effects. These characteristics could make propofol valuable as an induction agent in patients with limited or no cardiac reserve.

Methods: Approval was received from the Institutional Review Board for Human Research, and permission obtained from 30 ASA Class III patients at the time of the preoperative visit. Patients were randomly allocated to receive comparable induction doses of propofol (2.5 mg/kg), etomidate (0.3 mg/kg) or thiopental (4 mg/kg) and were premedicated with lorazepam 2-4 mg p.o. ninety minutes prior to induction of anesthesia. Upon arrival in the operating room, a radial arterial cannula, 14-gauge peripheral intravenous infusion and a triple lumen thermodilution pulmonary artery catheter were all inserted under local anesthesia. Patients were then given 100% oxygen for five minutes before baseline systemic, pulmonary arterial, central venous (CVP) and pulmonary capillary wedge pressures (PCWP) were measured; cardiac output and heart rate (HR) determined and cardiac index (CI) and pulmonary and systemic vascular resistances (PVR and SVR respectively) calculated. After this the induction agent was administered over a thirty second interval through the side-arm of the PA catheter introducer and followed by vecuronium (0.1 mg/kg). Ventilation was initially assisted and then controlled to maintain an end-tidal CO_2 concentration between 35 and 45 mmHg. Cardiovascular dynamics were re-measured every minute for the first four minutes after administration of the induction agent. Following this fentanyl (10 μg/kg) was injected and a minute later a repeat set of hemodynamics recorded followed by endotracheal intubation. Cardiovascular dynamics were recorded again five minutes after endotracheal intubation. Data were analyzed for statistical significance using analysis of variance and t-test with Bonferroni correction techniques.

Results: All baseline hemodynamics were similar in the three groups. HR was unchanged with propofol and etomidate but significantly increased (18%) with thiopental. Propofol (P) and thiopental (T) caused significant decreases in CI (P=11-17%, T=4 12%), systolic and diastolic arterial blood pressures (P=12-32%, T=9-23%); CVP (P=16-29%, T=4-8%); and PCWP (P=35-44%, T=9-13%) while etomidate did not change CI, arterial blood pressure or PCWP and slightly increased CVP (8-17%). PVR and SVR were not significantly changed by any of the induction agents. Administration of fentanyl after induction resulted in significant decreases in HR, CI, systolic and diastolic arterial blood pressures and PCWP in all groups which persisted after endotracheal intubation. Fentanyl reduced PVR and SVR after propofol and thiopental but not after etomidate. Indeed PVR was significantly increased by fentanyl after etomidate. CVP was unchanged by fentanyl after propofol and thiopental but increased after etomidate. Myoclonus (non-specific muscle movements unassociated with laryngoscopy or tracheal intubation) occurred in 33% of patients receiving etomidate but was absent in the patients receiving propofol or thiopental.

Discussion: The results of this study demonstrate that propofol produces similar decreases in CI and arterial blood pressures to thiopental and in contrast to etomidate which results in little change in these and virtually all other hemodynamics in patients with little cardiovascular reserve. The data suggest that reductions of CI and arterial blood pressure after propofol are principally related to marked decreases in ventricular pressures (CVP and PCWP) and that propofol causes greater changes in these variables than thiopental. The results also show that fentanyl results in significant cardiovascular depression when administered after any of the induction agents. Our findings indicate that propofol should be used with caution in patients with limited cardiovascular reserve especially if the patients are hypovolemic or are to receive fentanyl.

Title: PLASMA MIDAZOLAM LEVELS IN NON-PREGNANT AND PARTURIENT WOMEN

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Introduction. Midazolam, the water-soluble benzodiazepine, is a useful adjuvant to epidural analgesia in labor. Its anticonvulsant properties may make it useful for control of eclamptic convulsions but its pharmacokinetics in the pregnant patients in active labor have not been investigated. We here report such a study.

Method. This study was approved by the Regional Ethical Committee and carried out on fit consenting patients who had not received any benzodiazepine within 48 hr. The dose of midazolam was standardised at 5 mg given intravenously over 10 sec to five groups of patients: 12 in early active labor; 20 of similar age undergoing lower abdominal gynecological operations of comparable duration (40-60 min) to Cesarean Section given midazolam 5 min before induction of general anesthesia; 16 undergoing Cesarean Section given the drug either 5 min or 3 hr before induction of general anesthesia. Parturients were all at term, having had uncomplicated pregnancies; laboring patients had a slow intravenous infusion of oxytocin (2-5 mU/min) and this was also given to half of the gynecological patients.

Venous blood samples were drawn at frequent intervals for the first 2 hr following drug administration for estimation of total midazolam. Maternal and umbilical vein samples were taken at delivery. The coefficient of variation of the method of analysis was 10% at 25 ng/ml and 4% at 400 ng/ml. Blood sampling was not continued beyond 2 hr because of inaccuracy of estimating low plasma midazolam levels.

Results. Table 1 gives the mean plasma levels in each series, while Figure 1 illustrates the most important of these. Patients in early labor had significantly higher plasma levels for the first 45 min compared to the other groups ($P < 0.03-0.001$) and significantly higher than both Cesarean groups through the period of study. In the Cesarean patients (pooled data) these were significantly lower than in the non-pregnant patients ($P < 0.01-0.05$) throughout the period of study except for the first 5 min. Syntocinon did not affect the plasma levels in the gynecological patients. The umbilical vein/maternal vein midazolam ratios were related to the injection/delivery interval (Table 2).

Table 1. Mean plasma midazolam (ng/ml)

Min	2	5	10	15	30	45	60	90
L	411	321	230	170	101	76	46	31
G	215	159	127	106	71	53	45	32
GO	198	189	158	130	100	75	59	42
C190	210	166	134	101	60	47	40	35
C20	173	154	128	92	52	27	22	17

L= labor; G = gynecological operations±oxytocin(O); C= Cesarean Section with injection-delivery interval

Table 2. Neonatal umbilical vein (UV) to maternal vein (MV) ratios of midazolam at delivery

Procedure	Cesarean Section		Labor
Mean injection-delivery interval (min)	20	190	201
Mean UV/MV ratio	0.76	0.62	0.30

Discussion. The lower midazolam levels in the Cesarean Section patients may be due to the expansion of plasma volume and decreased plasma protein binding found in pregnancy. Placental transfer is less than with diazepam (1). The highly significantly raised plasma midazolam levels found in patients in active labor is an important finding which would limit its use as an anticonvulsant. It must be due to uterine contractions affecting liver blood flow with a high hepatic-extraction ratio drug.

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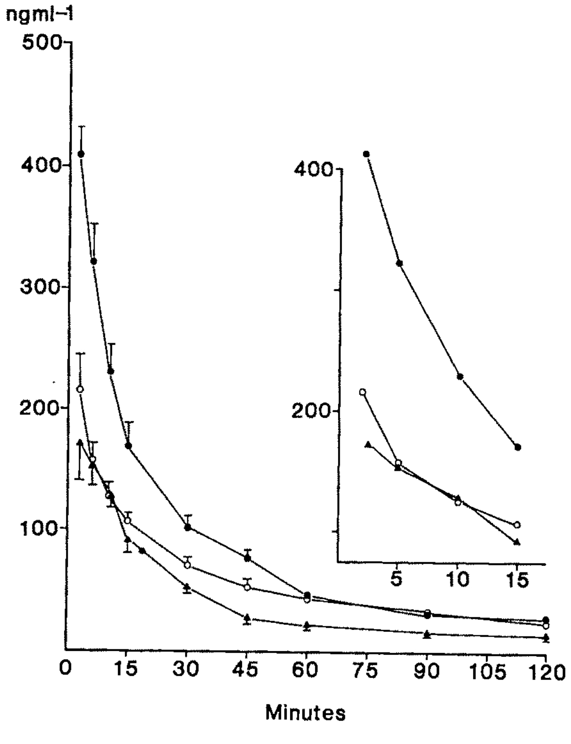
Figure 1. Mean (±SEM) plasma midazolam levels in patients in labor (●—●), elective Cesarean Section with midazolam given 20 min before delivery (▲—▲) and matched gynecological patients (o—o)



Title: NEGATIVE INOTROPIC EFFECTS OF BUPIVACAINE IN ISOLATED CARDIAC MUSCLE-MECHANISMS AND REVERSAL.

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Introduction. Cardiotoxic effects of bupivacaine (BUP) can be due to drug-induced impairment of electrical or mechanical function, or both. BUP was previously shown to slow conduction and suppress pacemakers,[1] but its effects on the mechanical function of the heart have not been well investigated. The present study was designed to evaluate the influence of BUP on the tension developed in isolated ventricular muscle and on calcium-dependent action potentials.

Methods. Papillary or trabecular muscles were isolated from the right or left ventricles of seven dog hearts. They were attached to an isometric force transducer and superfused in a small volume perfusion chamber with Tyrode's solution (4mM K^+, 2.5mM Ca^{++}, 37°C), which was gassed with 95% O_2 - 5% CO_2. Transmembrane action potentials were recorded with intracellular glass microelectrodes. Preparations were stimulated through bipolar electrodes at rates of 10/min or 60/min and exposed sequentially to BUP in concentrations of 1-10 mg/l for 10 to 30 min. Calcium-dependent potentials were induced in some preparations by increasing the extracellular K^+ concentration to 24mM (to inactivate Na^+ current), and the addition of 10^{-7} to 10^{-5}M epinephrine or isoproterenol (to stimulate the Ca^{++} current). Data were analyzed statistically by Student's "t" test (P 0.05 significant).

Results. Twitch tension was depressed by BUP (1, 2.5, 5, 10 mg/l) to 94%, 78%, 59% and 36% of its control value, respectively. The amplitude of calcium-dependent potentials was not changed by the above concentrations of BUP (Fig. 1). BUP suppressed the second and third peaks (induced by Ca^{++} released from sarcoplasmic reticulum) in biphasic or triphasic contractions, but caused little depression of the first peak which is due presumably to transmembrane calcium flow. In the same preparations, similar concentrations of BUP (5 mg/l) produced much more pronounced depression of tension at lower (10/min) than at higher (60/min) rates of stimulation (Fig. 2). However, decreases in excitability (skipped beats) occurred earlier in preparations stimulated at higher rates. The negative inotropic effects of BUP could be reversed by 0.1-1 mg/l epinephrine (Fig. 2) or mild respiratory alkalosis. However, an increase in extracellular calcium decreased excitability.

Discussion. BUP exerts direct negative inotropic effects on the heart muscle. They are not due to the inhibition of transmembrane inward calcium current, but are probably secondary to the inhibitory effects of the drug on some intracellular sites responsible for the regulation of contractile force (sarcoplasmic reticulum?). Catecholamines which improve intracellular calcium turnover can overcome the negative inotropic effects of BUP. Attempts at reversal by increasing extra-cellular calcium may be deleterious and produce more serious arrhythmias.

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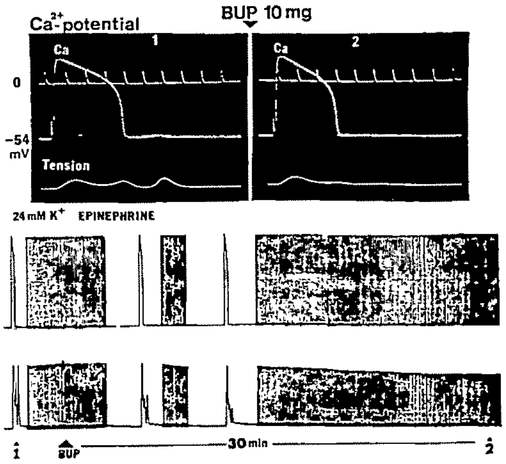

FIG. 1 - Effects of BUP (10 mg/l) on calcium-dependent potentials and tension; photographed from the oscilloscope screen (upper panel) and recorded at slow speed on the polygraph (lower panel).

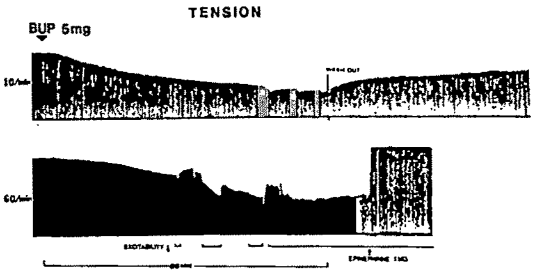

FIG. 2 Effects of BUP (5 mg/l) on tension developed by the preparation stimulated at a rate of 10/min (upper panel) and then at 60/min (lower panel). Note the initial decline in tension is slower at 60/min but is interrupted by periods of rapid decline (when the preparation becomes less excitable and responds to every second stimulus) and recovery (when the stimulus strength is raised to restore 1:1 response).

Title: THE EFFECT OF ANESTHETIC TECHNIQUES ON PERIOPERATIVE FLUID REQUIREMENT DURING CORONARY ARTERY BYPASS SURGERY

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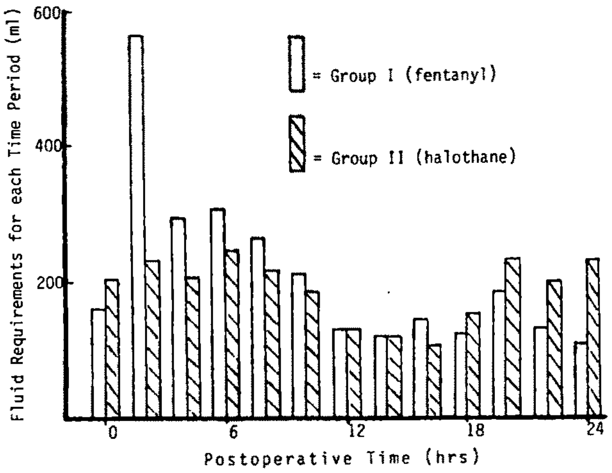
Introduction. It is commonly accepted amongst anesthesiologists and cardiac surgeons that, due to its venodilating action, morphine anesthesia for open heart surgery necessitates large fluid requirement. Previous studies has confirmed this, comparing morphine and halothane.[1] Fentanyl, a synthetic narcotic purportedly has less of this vasodilatory action. Therefore, this study was designed to compare the perioperative fluid requirements in patients undergoing elective coronary artery bypass graft (CABG) surgery utilizing either a fentanyl or halothane anesthesia technique.

Methods. Twenty-four patients undergoing elective CABG were entered into this institutionally-approved study. All had good left ventricular function (ejection fraction >50%), and all were free from hepatic and renal disease. The patients were randomly assigned to one of two groups. Anesthesia for Group I (n=11) consisted of fentanyl 75 µg.kg^{-1} bolus infusion followed by 0.3 µg.kg^{-1}.min^{-1} infusion. Anesthesia for Group II (n=13) consisted of diazepam 10 mg i.v. for induction and halothane 0.5-2.0% in oxygen for maintenance. Both groups received pancuronium bromide for intubation and maintenance of paralysis. Hypothermic, non-pulsatile cardiopulmonary bypass with non-blood prime was used in all cases. Perioperative fluid administration was guided by pulmonary artery diastolic pressure. Banked blood tranfusion was administered when hemoglobin level fell below 7 grams %. The amount of fluid and/ or blood required was recorded every two hours intraoperatively and for 24 hours postoperatively. The body weight was recorded preoperatively and 24, 48 and 72 hours later. The results were analyzed using non-parametric statistics.

Results. The two groups were not different in age, sex distribution, body surface area baseline cardiac output, or duration of cardiopulmonary bypass. During the intraoperative period, there was no difference between the groups in the total volume and type of fluid administered. Postoperatively, during the first six hours, Group I (fentanyl) required significantly larger amount of fluid ($p < 0.05$) (Figure 1). In addition, Group I also received more fluid in the form of colloids. By the end of 24 hours, however, there was no difference between the two groups in the total amount of fluid required. Average weight gain after the same period was also not different.

Discussion. The only significant difference between the two groups was a transient increase in fluid requirement by the fentanyl group (Group I) during the first six hours postoperatively. Since the pulmonary artery diastolic pressure was used as the sole guideline to fluid therapy, this difference in fluid requirement represents a decreased pre-load in Group I patients. The reason for this relative decrease in pre-load and its short duration is unclear. It is not correlated with body temperature changes postoperatively (which were identical in both groups). Since fentanyl at this dose range persists in the body much longer than 4-6 hours, it is unlikely that it alone caused this transient decrease in pre-load. One possible explanation may be that all patients in Group I received postoperative positive pressure ventilation, whereas none in Group II did. Positive pressure ventilation, by impeding venous return, decreases pre-load.[2] This effect is usually countered by increasing fluid loading initially. Overall, this study shows that fentanyl, unlike morphine, does not necessitate larger blood or fluid requirement than halothane for open heart surgery.

Figure 1: 24-hour Postoperative Fluid Requirements of CABG Patients



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TITLE: EFFECT OF RANITIDINE ON INTRAGASTRIC pH IN CHILDREN

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INTRODUCTION: Ranitidine is a H_2 histamine receptor antagonist which inhibits gastric acid secretion in the stomach. Its effectiveness in decreasing gastric acidity has been well documented in adults.[1] However, its efficacy in children prior to anesthesia has not been evaluated, nor has an effective dose been established.

METHODS: The protocol for this study was approved by our institutional review board and written consent was obtained from the parents. Forty children, 3 to 14 years of age (mean±S.E. 7.7±0.6 years), were studied. The mean weight of the children was 30.0±2.3 kg. The children were randomly divided into five groups. Group I acted as control and did not receive ranitidine preoperatively. Group II received 2.0 mg/kg po ranitidine, Group III received 2.5 mg/kg po ranitidine, Group IV 3.0 mg/kg po ranitidine, and Group V received 3.5 mg/kg of ranitidine. The five groups of children were comparable in age, weight and type of surgical procedure.

Ranitidine was prepared in the pharmacy by soaking tablets in distilled water and mixing them with sucrose solution. The drug was administered as an oral suspension in a concentration of 5 mg/ml at least one hour prior to surgery.

Premedication in children less than 7 years of age consisted of rectal methohexital (20-25 mg/kg) administered 20 min before surgery. None of the children received anticholinergic drugs, narcotics or antibiotics preoperatively. The anesthetic technique consisted of halothane $N_2O:O_2$ with endotracheal intubation.

After satisfactory induction of general anesthesia, a #18 Salem sump tube with an intraluminal pH micro-electrode was inserted orally into the stomach. Position of the tube was confirmed by auscultation over the epigastrium while rapidly injecting air into the tube, by aspiration of gastric contents, and by observing the epigastrium for an indentation produced by the gastric tube. The gastric contents were collected with an aspirating trap and suction.

The volume and color of gastric juice was noted. The intragastric pH was measured by a Corning digital mini-pH meter M-103 (#1428) and standard microelectrodue M1-506 (#14691) which was calibrated against standard buffer solution before each set of measurements. The pH was also determined by pHydroin paper. Statistical analysis was performed using the non-differentiated students t-test and analysis of variance.

RESULTS: The results of the gastric pH measured by the pH meter, H^+ concentration and volume of gastric juice ml/kg body weight are summarized in Table 1.

	pH	H^+conc (mol/l)	Vol (ml/kg)
Group 1 (n=8)			
M±S.E.	2.0± .3	18.7± 5.1	.31± .07
Range	1.4-3.7	.2-39.1	.01- .57
Group II (n=8)			
M±S.E.	5.1± .5**	1.25±1.25*	.10± .05
Range	2.0-7.4	3.91×10^{-5}-10	.01- .42
Group III (n=8)			
M±S.E.	6.1±0.2**	$1.9\times10^{-3}\pm9\times10^{-4}$*	.29± .08
Range	5.1-6.9	.0001-.008	.01-0.62
Group IV (n=8)			
M±S.E.	5.4±0.6**	2.50± 2.50	.31± .13
Range	1.7-7.4	3.9×10^{-5}-20	.01-1.1
Group V (n=8)			
M±S.E.	6.3±0.5**	.04±.04	.11± .04
Range	3.6-8.6	2.5×10^{-6}-0.3	.01- .28

* Significant difference from control $p<0.01$
** $p<0.001$

In the present study with direct intragastric pH measurements, preoperative oral ranitidine at doses of 2.0 mg/kg to 3.5 mg/kg effectively raised intragastric pH in the children studied. Increasing the dose of ranitidine above 2.0 mg/kg did not produce a significant difference in intragastric pH between the groups studied. The effect on gastric volume was inconsistent.

All children who received ranitidine were protected against the major complications of acid aspiration, because none had an intragastric pH less than 2.5 and a gastric volume more than 0.4 ml/kg. In the present study ranitidine proved to be as effective as cimetidine in decreasing gastric acidity in children.[2] In contrast to cimetidine, ranitidine has minimal effects on the cytochrome P450 enzyme system of the liver, which may make its use advantageous in children on multiple drug regimens.[3] The longer duration of action of ranitidine eliminates the need for repeated doses.

In regard to the dose of ranitidine in children, the 2.0 mg/kg dose is as effective as higher doses in decreasing gastric acidity. Because no further decrease in either gastric acidity or volume was seen with higher doses, we recommend 2.0 mg/kg po ranitidine as prophylaxis against acid aspiration in children.

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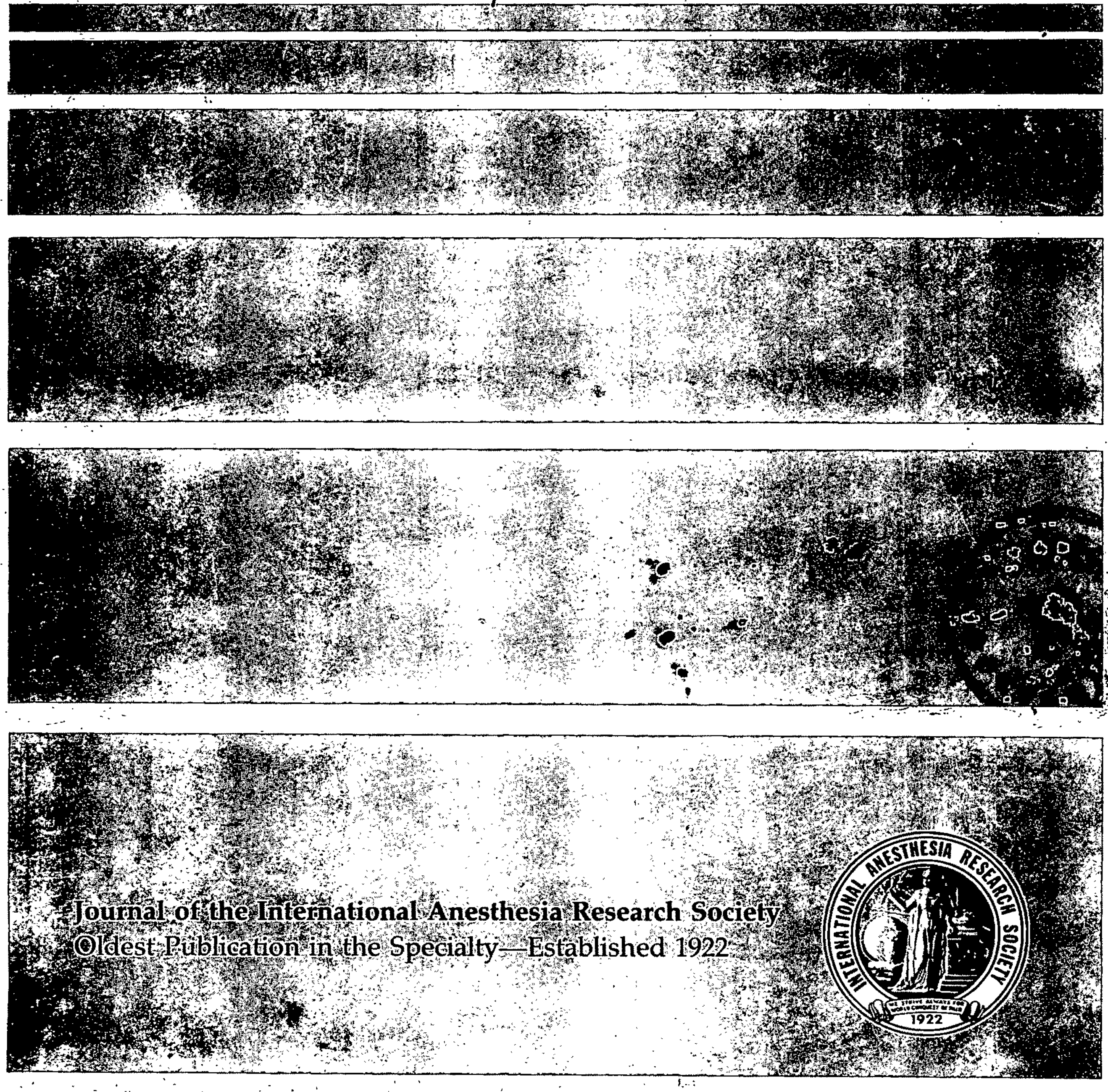

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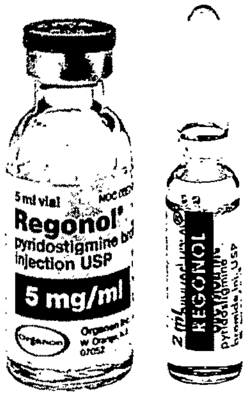

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When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

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THE SUFENTA® REPORT

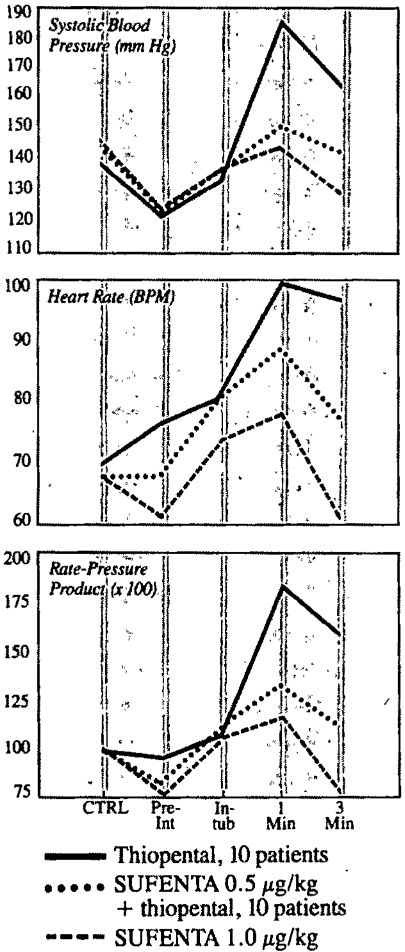
A PRACTICAL ANESTHESIA UPDATE

VOL. 1, NO. 1 JANSSEN PHARMACEUTICA INC. WINTER 1986

LESS BARBITURATE, BETTER STABILITY WITH LOW-DOSE SUFENTA®

SAN FRANCISCO: Low doses of SUFENTA® (sufentanil citrate) Injection Ⓒ, given prior to thiopental as an adjunct to induction, improved hemodynamic stability and reduced barbiturate requirements, according to a study presented here at the 1985 Annual Meeting of the A.S.A. In a group of 30 adult patients who underwent surgery of 25 min. to 8.5 hr. duration, thiopental was used for induction, either alone or combined with SUFENTA. SUFENTA (0.5 or 1.0 μg/kg) reduced thiopental requirements by 50% to 68%, respectively, and the hemodynamic response to laryngoscopy and intubation was attenuated, as measured by systolic pressure, heart rate and rate-pressure product. Bradycardia, truncal rigidity and recall were not observed.

Better Hemodynamic Control



(Abstracted from Brizgys, Morales and Owens, *Anesthesiology* 1985; 63:A377)

Experience With 93 Patients Generates "Thumbnail" Dosage Guidelines

Clinical experience with SUFENTA in general surgery revealed that *total dosage requirements averaged about 1 μg/kg/hour or less,* in surgery up to 8 hours.

In the same patients the *induction dose averaged about 75% of total dose.* The remainder was given in incremental maintenance doses as needed.

The induction dose of SUFENTA administered prior to intubation reduces hypertension and tachycardia.

In every case, however, dosage should be titrated to individual patient needs.

NOW SHOWING: AN INFORMATIVE 22-MINUTE FILM

Benjamin J. Kripke, MD, and Edson O. Parker III, MD, are featured in the medical film "SUFENTA: A Practical Guide for General Surgical Procedures." The anesthesiologists demonstrate, through actual hands-on experience, how careful dosage planning provides maximal hemodynamic stability throughout the entire procedure. To arrange a viewing of this film, please contact your local Janssen Representative.

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Adult Dosage Recommendations: A Summary

Please see full Prescribing Information, including dosage, on next page.

	General Surgical Procedures	Major Surgical Procedures
Expected Duration	1 to 2 hours	2 to 8 hours
Types of Procedures	Total vaginal hysterectomy, gall bladder surgery, bilateral inguinal hernia repair, open reduction of fractures	Major orthopedic surgery, carotid endarterectomy, nephrectomy, major abdominal surgery (e.g., colectomy)
Recommended Induction Dose	1 to 1.5 µg/kg (1.4 to 2.1 ml for a 70 kg patient), administered with N_2O/O_2, endotracheal intubation and mechanical ventilation	1 to 5 µg/kg (1.4 to 7 ml for a 70 kg patient), administered with N_2O/O_2, endotracheal intubation and mechanical ventilation
Recommended Maintenance Dose	10 to 25 µg (0.2 to 0.5 ml) based upon changes in clinical signs and patient's response to initial dose	10 to 25 µg (0.2 to 0.5 ml) based upon changes in clinical signs and patient's response to initial dose
Total Dosage	For cases lasting 2 hours, would not be expected to exceed 2 µg/kg (2.8 ml for a 70 kg patient) when used with N_2O/O_2	For cases lasting 8 hours, would not be expected to exceed 8 µg/kg (11.2 ml for a 70 kg patient) when used with N_2O/O_2

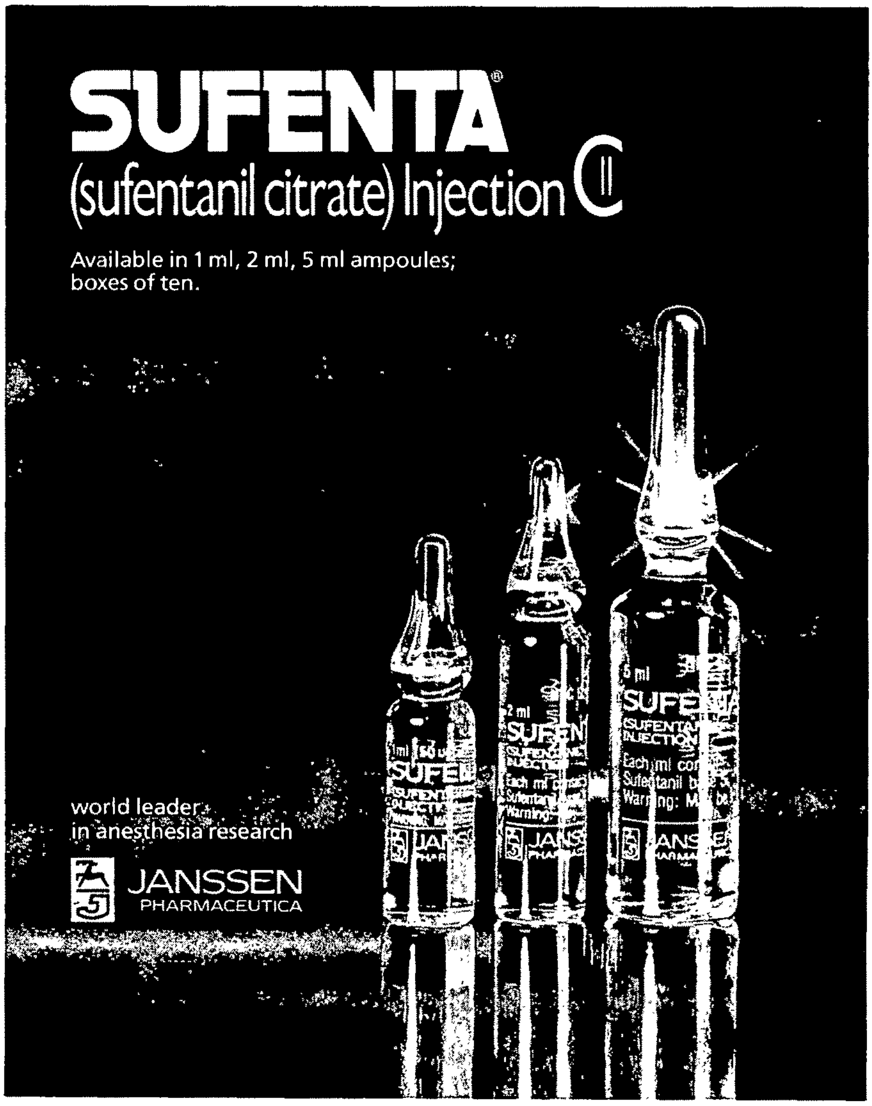
SUFENTA® BRIEFCASE

Putting SUFENTA to Work in Your Practice

In actual clinical practice, when used in balanced general anesthesia, SUFENTA is about 10 times as potent as fentanyl. Thus, 1 ml SUFENTA (50 µg/ml) is equivalent to 10 ml fentanyl (50 µg/ml).

Because of this potency difference, less volume of drug is needed, making it especially convenient for use in cardiovascular surgery and longer procedures. For accurate dosage calibration in shorter procedures, a tuberculin syringe, a 2 ml insulin syringe or dilution may be helpful.

In a laboratory study, SUFENTA has been found to be compatible and stable in solution with 5% glucose in water, 5% glucose in normal saline, lactated Ringer's solution and normal saline (tested in plastic containers refrigerated at 4°-8°C for 24 hours followed by 48 hours at room temperature).


SUFENTA®
(sufentanil citrate) Injection CII
Available in 1 ml, 2 ml, 5 ml ampoules; boxes of ten.
world leader in anesthesia research
JANSSEN PHARMACEUTICA

SUFENTA® (sufentanil citrate) Injection CII

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

CLINICAL PHARMACOLOGY: SUFENTA is an opioid analgesic. When used in balanced general anesthesia, SUFENTA has been reported to be as much as 10 times as potent as fentanyl. When administered as a primary anesthetic agent with 100% oxygen, SUFENTA is approximately 5 to 7 times as potent as fentanyl. (See dosage chart for more complete information on the use of SUFENTA.) At doses of up to 8 µg/kg, SUFENTA provides profound analgesia; at doses ≥8 µg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 1.4 minutes, redistribution of 17.1 minutes and an elimination half-life of 164 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with equipotent dosages of fentanyl. At dosages of SUFENTA of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 µg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA-nitrous oxide/oxygen produced reductions in cerebral blood flow comparable to those of enflurane-nitrous oxide/oxygen. During cardiovascular surgery, SUFENTA-oxygen produced EEG patterns similar to fentanyl-oxygen; these EEG changes were judged to be compatible with adequate general anesthesia.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Skeletal muscle rigidity is related to the dose and speed of administration of SUFENTA. This muscular rigidity may occur unless preventative measures are taken (see Warnings).

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate)is indicated:

as an analgesic adjunct in the maintenance of balanced general anesthesia.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compro-mised-respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: *There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such* use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

Usage In Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 µg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART

TOTAL DOSAGE	MAINTENANCE DOSAGE
ADMINISTRATION WITH NITROUS OXIDE/OXYGEN FOR SURGICAL PROCEDURES LASTING UP TO EIGHT HOURS: **• TOTAL DOSAGE REQUIREMENTS OF 1µG/KG/HR OR LESS ARE RECOMMENDED**	
1-2 µg/kg: Expected duration of anesthesia 1-2 hours. Approximately 75% or more of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	**10-25 µg (0.2-0.5 ml):** as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to remaining operative time anticipated.
2-8 µg/kg: Expected duration of anesthesia 2-8 hours. Approximately 50 to 75% of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	**10-50 µg (0.2-1 ml):** as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
ADMINISTRATION WITH 100% OXYGEN	
8-30 µg/kg: (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 µg/kg, catecholamine release is attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	**25-50 µg/kg (0.5-1 ml):** as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of SUFENTA accurately, the use of a tuberculin syringe or equivalent is recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

NDC 50458-050-01	50 µg/ml, 1 ml ampoules in packages of 10
NDC 50458-050-02	50 µg/ml, 2 ml ampoules in packages of 10
NDC 50458-050-05	50 µg/ml, 5 ml ampoules in packages of 10

Protect from light.
Store at room temperature.

JANSSEN
PHARMACEUTICA

Janssen Pharmaceutica Inc.
Piscataway, NJ 08854

U.S Patent No. 3,998,834
7618503-M
May 1984, January 1986

Continuous O_2/CO_2 Monitoring Report #1

Subject: Simple, low-cost pulse oximetry monitoring for timely hypoxemia detection.

Pulse Oximetry
NOVAMETRIX 500

Pulse oximetry is a noninvasive technique for assessing patient oxygenation.

An oximeter determines percentage hemoglobin saturation by measuring the absorbency of two different wavelengths of light passed through a pulsating arterial vascular bed. By comparing the ratios of the pulse amplitudes from each light, SaO_2 may be calculated under a wide range of hemodynamic conditions.

The use of pulse oximetry during routine anesthesia allows early recognition of hypoxemia permitting quick response to improve oxygenation.

Accurate and reliable, pulse oximetry represents a significant advance in anesthesia monitoring. In designing the Model 500 Pulse Oximeter, Novametrix retained the accuracy and reliability of earlier units, but added two vital elements: ease of use and low cost.

The microprocessor-controlled Novametrix 500 Pulse Oximeter needs no calibration or warm-up. Its digital electronic circuitry is entirely maintenance-free.

Setup is fast. Just push the power switch and the unit performs a quick self-diagnostic check. Then the 500's programmed menu quickly helps you set the high and low SaO_2 and pulse rate limits. Once the limits are set they are constantly visible. And the Novametrix 500 keeps them in memory indefinitely—for weeks or even months—until you decide to change them.

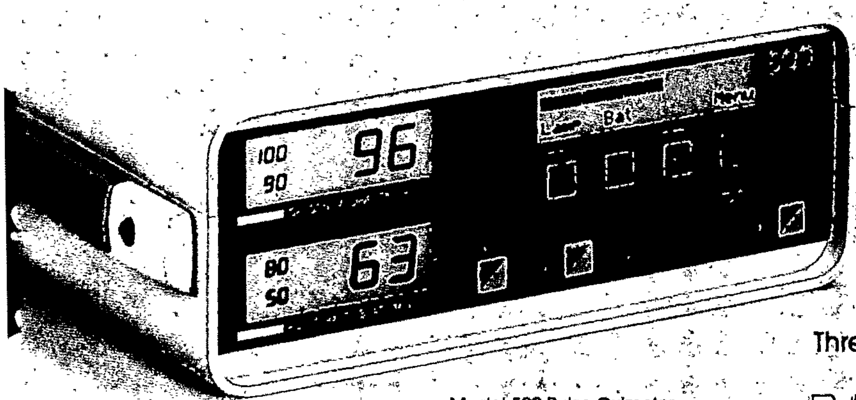
> ***"The Novametrix 500 is a simple, inexpensive means of monitoring oxygenation to reduce the incidence of anesthetic mishap during routine procedures."***

Operation is just as simple, with easy-to-read displays of O_2 saturation and pulse rate. A message center displays a bar graph of pulse amplitude as well as providing specific information regarding any alert condition. In addition, there's an audible pulse signal that changes in tone—up or down to reflect changes in SaO_2—so you can keep your eyes on the patient.

The Novametrix 500 Pulse Oximeter is small, lightweight (under 10 lbs.), and operates for a full 20 hours on a single battery recharge. (Not just an hour or two of battery backup power like most other oximeters.)

Novametrix finger, ear, and versatile flexible sensors are small, ruggedly built, and designed for easy application to patients of all ages. And Novametrix' unique selectable response time eliminates false alerts due to motion artifact.

For full technical details—and the surprisingly low price—write Novametrix Medical Systems Inc., 1 Barnes Industrial Park Road, P.O.Box 690, Wallingford, CT 06492. Or call us toll-free at 1-800-243-3444.



Model 500 Pulse Oximeter.

Pulse Oximetry.
End Tidal CO_2.
Transcutaneous O_2/CO_2.
Three technologies...one source.

NOVAMETRIX

60th CONGRESS
T. H. SELDON DISTINGUISHED LECTURE

"Excellence Achieved"

To be presented Monday, March 17, 1986 by

J. Alfred Lee, FFARCS, FFARCS (I)

Honorary Consulting Anaesthetist
to the Southend-on-Sea Hospital
Essex, England

If anesthesia had an Olympiad, Dr. J. Alfred Lee would be a three-time medalist, having been thusly honored by the Royal Society of Medicine, the Royal College of Surgeons, and the European Society of Regional Anesthesia.

These honors derive from his long and distinguished career: as a consultant anesthetist at the Southend General Hospital, where he founded Britain's first Anaesthetic Out-Patient Clinic in 1948, and its first Postoperative Observation (Recovery) Room in 1959; as a prolific author—his works include "The Synopsis of Anaesthesia," now in its tenth edition; and as president of the Anaesthetics Section of the Royal Society and of the Association of Anaesthetists of Great Britain and Ireland.

The Lecture title was deliberately chosen by Dr. Lee as a "sequel" to the 1985 Seldon Lecture entitled "Standards for Excellence." As a scholar who "would like to be known as a clinical anaesthetist," we know he will feel very much at home with the audience he will address at our 60th Congress.

T. H. Seldon, MD, FFARCS(I)

Rochester, Minnesota/Sun City, Arizona

In addition to his long tenure as Editor of *Anesthesia and Analgesia,* Dr. Harry Seldon served as Program Chairman for 15 of the 60 IARS Congresses. Not only will the Diamond Anniversary meeting be special to him on that account, but it will allow a "class reunion" of sorts with Dr. Lee. They last met in 1970 when both were made Honorary Fellows of the Faculty of Anaesthetists of the Royal College of Surgeons (Ireland).

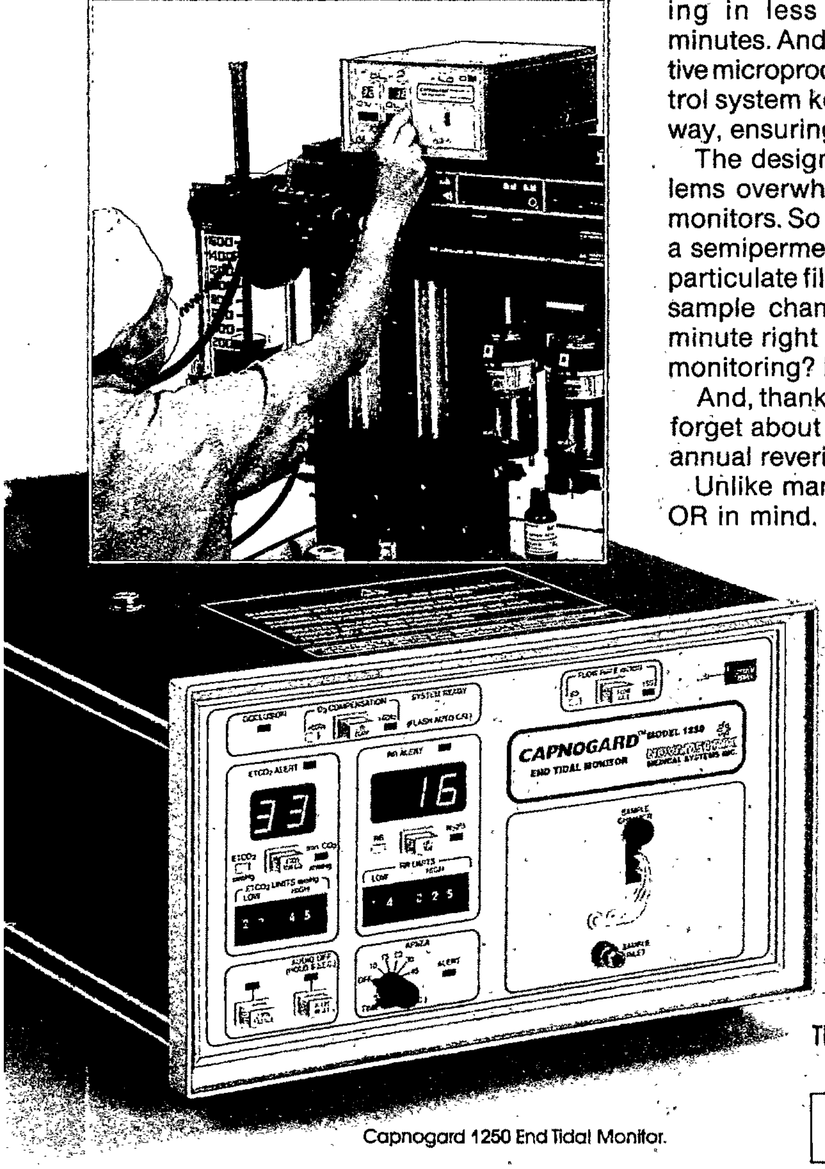
Continuous O_2/CO_2 Monitoring Report #2

Subject: Cost-effective capnography for the OR; calibration and condensation problems solved.

End Tidal CO_2
NOVAMETRIX 1250

The measurement of end tidal carbon dioxide by a modern on-line analyzer provides a close approximation of alveolar partial pressure of CO_2.

Continuous measurement of $ETCO_2$ in the OR allows up-to-the-minute assessment of the adequacy of ventilation, and assists in the timely diagnosis of intraoperative problems or metabolic trends allowing early intervention to prevent adverse outcome.



Capnogard 1250 End Tidal Monitor.

"An end tidal monitor you don't need to calibrate? Yes. The Capnogard 1250 from Novametrix."

Capnography in the OR used to mean long warm-up periods, tedious calibration sessions, and a constant struggle to keep the sampling circuit clear of moisture.

Thanks to microelectronic technology, this is no longer the case. And none of the newer $ETCO_2$ monitors use this technology better than the Novametrix 1250.

But while the electronics of the Capnogard™ 1250 are complex, they actually make the monitor simpler to use. Push the system power switch and the unit is up and monitoring in less than two minutes. And its innovative microprocessor control system keeps it that way, ensuring continuous reliable operation.

The designers of the Capnogard noted how moisture problems overwhelmed the water traps of even the best end tidal monitors. So they developed a dehumidification interface kit with a semipermeable tube drying system and a built-in disposable particulate filter. Then they incorporated a front panel accessible sample chamber that could be manually cleared in under a minute right in the OR. Moisture a problem with your end tidal monitoring? Not if you're using the Capnogard 1250.

And, thanks to the 1250's unique auto-zeroing system, you can forget about time-consuming daily calibration sessions. (Semi-annual reverification of calibration is recommended.)

Unlike many CO_2 analyzers, the 1250 was designed with the OR in mind. So you'll find features like direct measurement of N_2O; automatic and continuous N_2O compensation; large LED readouts; apnea alert; two-minute silence, audio off, and alert reset buttons; sample exhaust for gas scavenging; and analog outputs for recorder and scope displays.

For details on the Capnogard 1250—and its surprisingly low price—write Novametrix Medical Systems Inc., 1 Barnes Industrial Park Road, P.O. Box 690, Wallingford, CT 06492. Or call us toll-free at 1-800-243-3444.

Pulse Oximetry.
End Tidal CO_2.
Transcutaneous O_2/CO_2.
Three technologies...one source.

NOVAMETRIX

Soothing news for busy anesthesiologists

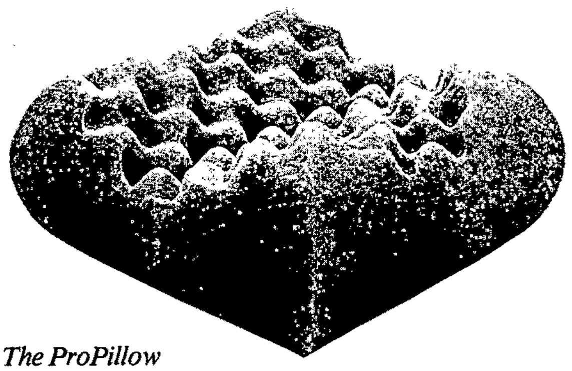
Dr. Smith was having another busy day in surgery. One Swan-Ganz placement had been unusually time-consuming. Plus the patient had been difficult to intubate. To top it off, the pump time had been excessive.

Down the hall, Dr. Jones had a marathon case involving a young woman undergoing a tuboplasty for infertility. Finally, 5½ hours later the surgeons were closing the skin. He heaved a sigh of relief and automatically leveled the table from the previous several hours where the Trendelenberg position had been necessary.

But these two stories don't end here. About 28 days later, *both patients had a bald spot about the size of a silver dollar at the occiput. . . exactly where their heads were resting on the table for hours on end.* They were each advised by their surgeons that they had a 50% chance of their hair growing back within the next year. But there was an equal chance that their hair wouldn't grow back at all. The anesthesiologists on both cases were never told of the problem.

The ProPillow takes the pressure off

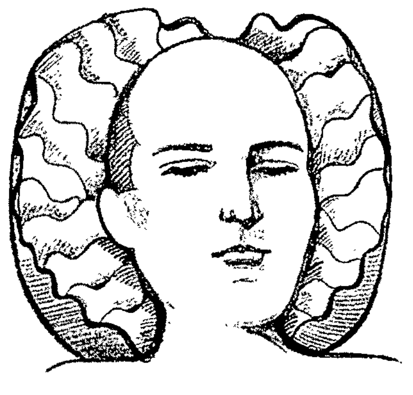
The ProPillow Anesthesia Pillow helps "take off the pressure" to the circulation of the face and scalp during prolonged anesthesia. It's unique "hills and valleys" construction creates a protective effect by evenly distributing the weight of the head and neck. Result: no more pressure in one area greater than any other area. And those precipitous swings in blood pressure are less likely to result in ischemia to the scalp. All this lessens the chance of post-op alopecia.



The ProPillow Anesthesia Pillow

The end of the juggling act

The ProPillow lets you off gracefully from attempts to juggle the heavy head (10 lbs.) during intubation. The ProPillow Anesthesia Pillow stabilizes (by gently gripping) the patient's head in the neutral, "sniffing", position. It even helps free up one of your hands when you're using a mask for short cases.



The ProPillow Anesthesia Pillow stabilizes the head, supports the neck and helps take the pressure off.

An eye for details

Awake patients really appreciate the comfort of the ProPillow Anesthesia Pillow. Especially the eye patients who are undergoing removal of cataracts with intra-ocular lens implants. And the ProPillow fits inside the frame used by Opthalmologists during this tedious microsurgery. Less squirming. . . and possibly sedation required.

And the price is right

Because of the ProPillow's reasonable price, some say we should call it disposable. But it is made to last for up to 50 cases. You can use a nurse's bouffant cap to cover the ProPillow. Or even spot wash and air-dry it. It's made from a bright blue, breathable, resilient polyurethane foam that's 100% non-allergenic and non-irritating to skin.

It's easy to order the ProPillow Anesthesia Pillow! Call us **TOLL FREE** at **(800) 227-0517 outside California**, or **(800) 554-5541 inside California.** Or, give this page to your head nurse or purchasing agent to get the ProPillow promptly. We ship within 24 hours. *Pediatric Size available, ask for details.

ProTechPacific
1221 Andersen Drive
San Rafael, CA 94901

Makers of the **ProPillow Anesthesia Pillow, NECK-PIL-O Neck Support Pillow, DIXSEY Hip Abduction pillow** and the new **STRAPEZE *Velcro Endotracheal Tube stabilizer.**

Continuous O_2/CO_2 Monitoring Report #3

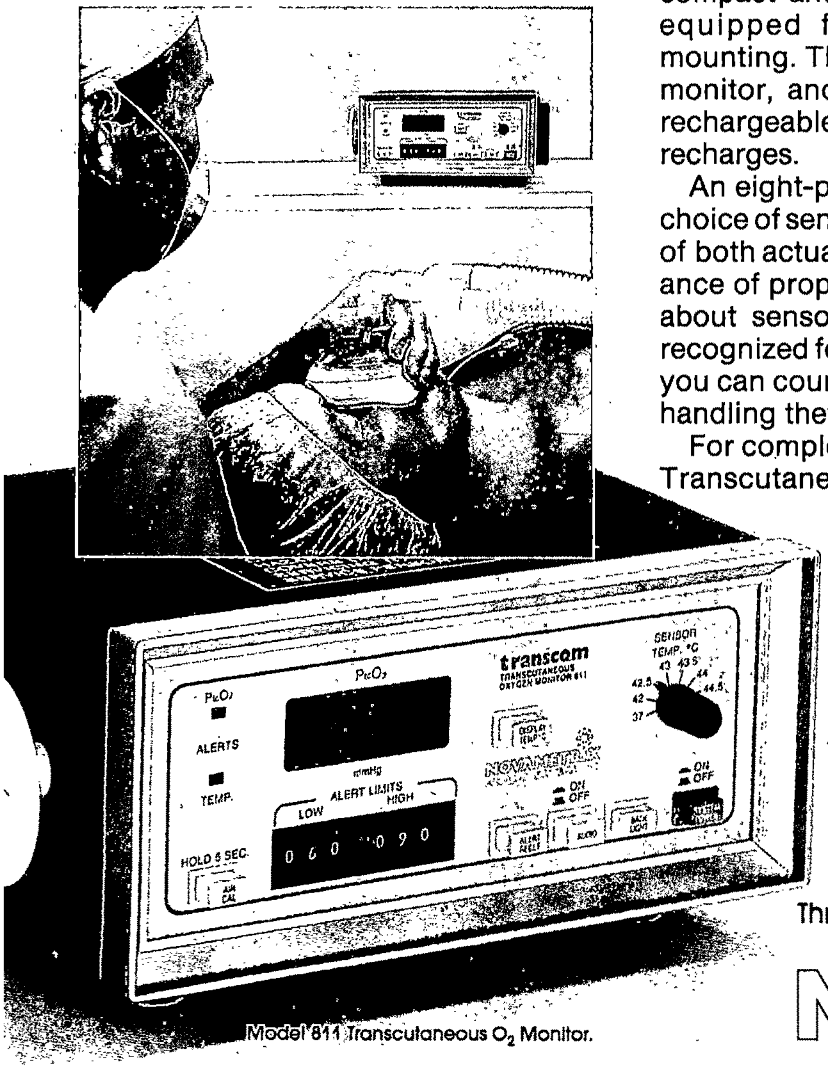
Subject: Compact, easy-to-use $P_{tc}O_2$ monitoring for OR patients.

3

NOVAMETRIX 811

"$P_{tc}O_2$ is a useful variable because it is a noninvasive 'global' monitor of patient oxygenation. It can give an early warning of decreasing oxygen delivery, thus allowing the treatment of impending hypoxia before it occurs."[1]

"$P_{tc}O_2$ monitoring proved also to act as an early warning device for impending hypoxemia and hemodynamic compromise, thereby facilitating very early therapeutic intervention."[2]



Model 811 Transcutaneous O_2 Monitor.

Along with a growing recognition of the usefulness of continuous gas monitoring during surgery came the need for a cost-effective $P_{tc}O_2$ monitor suitable for routine use on patients in the OR. The Novametrix 811 monitor meets that need.

Simplicity is a key feature of the Novametrix 811. Activate the system power switch, push the automatic air calibration button, and you're ready to monitor.

And Novametrix knows that space is scarce in a crowded OR, so the 811 is compact and can be equipped for pole mounting. The 811 is also a true portable transcutaneous monitor, and may be operated on AC power or on its rechargeable gel cell for up to eight hours between recharges.

> ***"The Novametrix 811 is the first transcutaneous monitor to deal with the special requirements of all OR patients."***

An eight-position temperature selection switch offers a choice of sensor temperatures for operation. Visual display of both actual and selected temperature provides reassurance of proper sensor operation. And while we're talking about sensors, remember that Novametrix sensors are recognized for their rugged construction and durability, so you can count on their withstanding the occasional rough handling they'll receive in the OR.

For complete information on the Novametrix Model 811 Transcutaneous O_2 monitor, along with details on its surprisingly low price, call us toll-free at 1-800-243-3444. Or write Novametrix Medical Systems Inc., 1 Barnes Industrial Park Road, P.O. Box 690, Wallingford, CT 06492.

Pulse Oximetry.
End Tidal CO_2.
Transcutaneous O_2/CO_2.
Three technologies...one source.

NOVAMETRIX

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[1] Barker, S. M.D., Ph.D. and Tremper, K. M.D., Ph.D. *Journal of Clinical Monitoring, 1:* 130-134 (1985).

[2] Chubra-Smith, N.M. M.D., et. al. *Anesthesia/ Analgesia 64:* 185-304 (1985).

Anaquest

introduces

Enlon®

(edrophonium chloride
injection, USP)

**A rapid-acting
neuromuscular reversal agent**

**From the developers of
Ethrane® (enflurane) and Forane® (isoflurane)**

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019 800 ANA DRUG
A Division of BOC Inc

60-second reversal

of neuromuscular blockade

- **Onset of reversal significantly faster than with neostigmine or pyridostigmine**—60 seconds versus 7 minutes for neostigmine, 12 minutes for pyridostigmine.[1,2]
- **Duration of reversal comparable to that of neostigmine**—66 minutes versus 76 minutes for neostigmine.[1,2]*
- **Significantly fewer muscarinic side effects and lower atropine requirement than with neostigmine**—edrophonium, 0.5 mg/kg, with only 7 μg/kg atropine, produced minimal change in heart rate or mean arterial pressure compared to noticeable changes in both indexes following neostigmine, 0.04 mg/kg, using *twice* the atropine dose (15 μg/kg).[1,2]
- **May be the preferred reversal agent for atracurium and vecuronium** "...compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and...antagonizes more rapidly residual atracurium-induced neuromuscular blockade."[3]

  "Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug."[4]

***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. Anesthesiology 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 54:375-385, 1982.

Please see use information on next page.

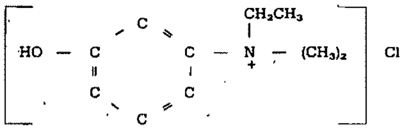
Anaquest

introduces

Enlon® (edrophonium chloride injection, USP)

DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution:

10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4.

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the mycneural junction.

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage. ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers: The safety of ENLON during lactation in humans has not been established.

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anticholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to hypotension;

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

OVERDOSAGE

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating; increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

DOSAGE AND ADMINISTRATION

The recommended adult intravenous injection for antagonism of neuromuscular block:

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:

Adults:

Intravenous Dosage: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dosage: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

Children:

Intravenous dose in children weighing up to 75 pounds:

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

Intravenous dose in children weighing above 75 pounds:

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.
Overtreated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

ENLON (edrophonium chloride injection, USP) Test in Crisis:

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

NDC 10019-873-15 15 mL multidose vials. 2-85

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019
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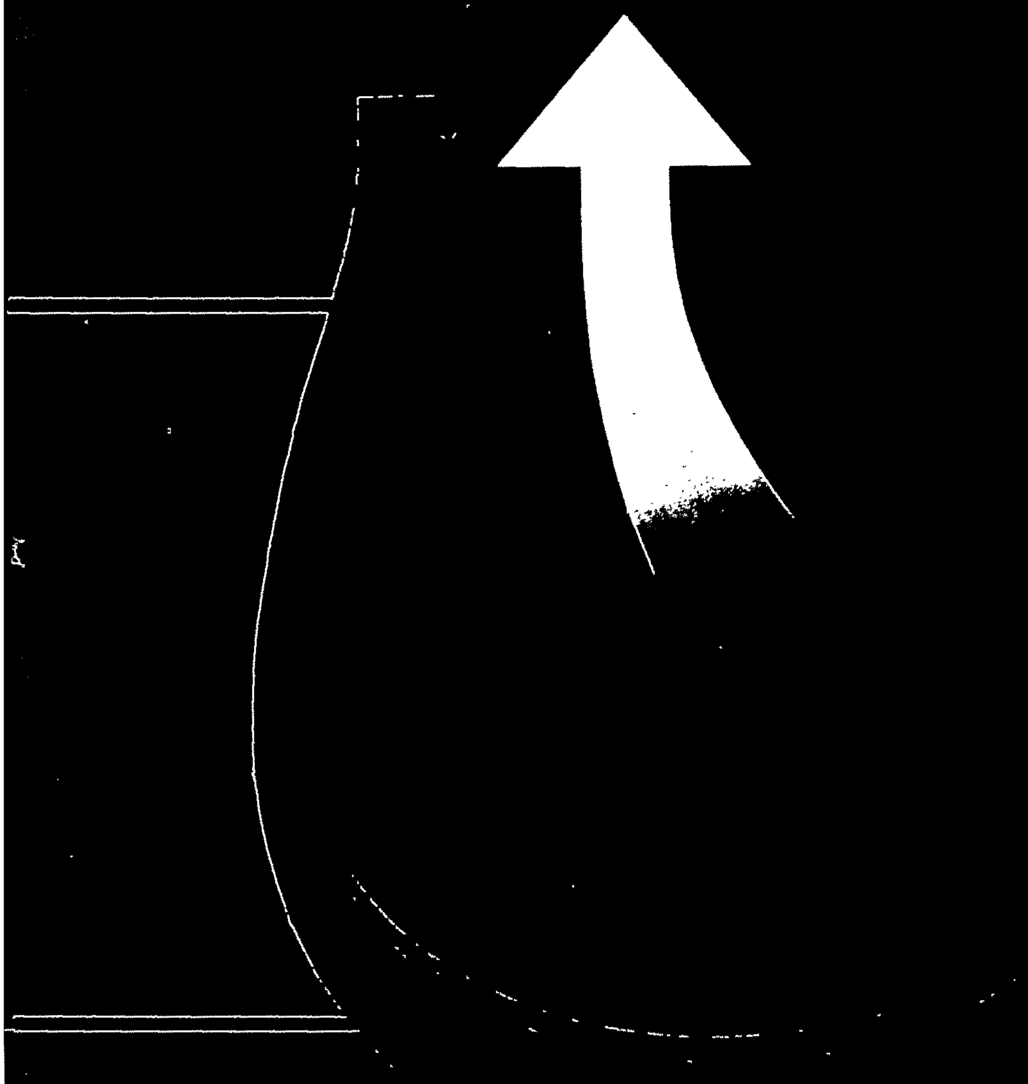


Instead of catecholamines

for the short-term management of heart failure

energy efficient

Inocor® I.V.

(AMRINONE)

A major advance toward better inotropic therapy

energy efficient
Inocor® IV
(AMRINONE)

Instead of catecholamines for the short-term management of heart failure

- Independent of the effects of digitalis and catecholamines
- Hemodynamics rapidly improved
- Heart rate and blood pressure not significantly changed... has not been shown to increase risk of arrhythmias (see precautions)
- Can be used in patients with myocardial ischemia
- Benefits sustained during therapy... no evidence of tachyphylaxis
- Easy to administer

Patients receiving INOCOR should be carefully monitored with the following laboratory studies: platelet counts, liver enzymes, fluid and electrolyte changes, and renal function. Hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

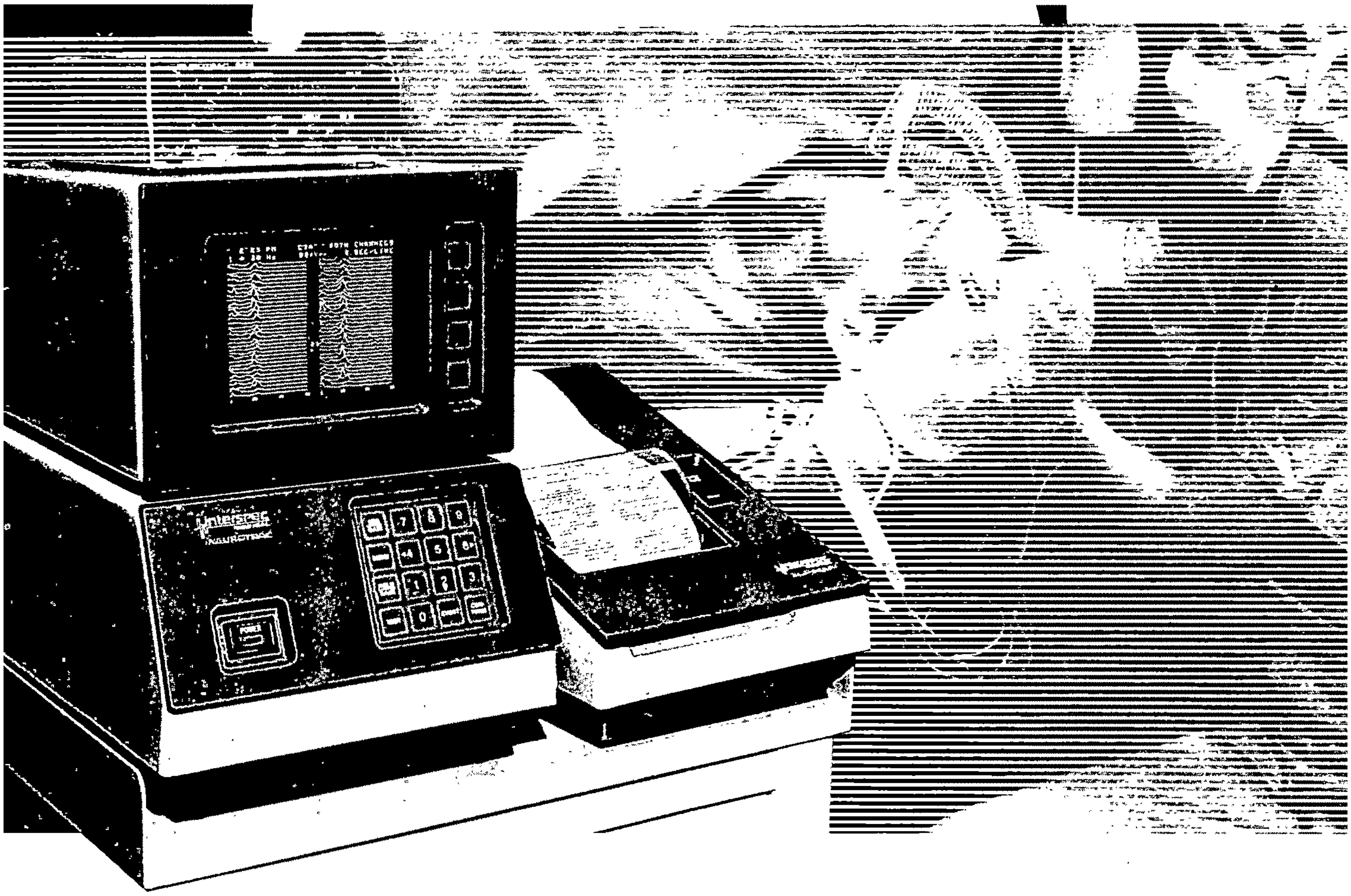
1. Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. *Circulation* 1980;62:28-34.

Please see brief summary of product information on this page for contraindications, adverse reactions, patient selection, and precautionary recommendations.

Winthrop-Breon
Winthrop-Breon Laboratories, Division of Sterling Drug Inc., New York, NY 10016 61065

INOCOR lactate injection, brand of amrinone lactate, represents a new class of ca
inotropic agents with vasodilator activity, distinct from digitalis glycoside
catecholamines.
INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-
management of congestive heart failure in patients who can be closely monitorec
who have not responded adequately to digitalis, diuretics, and/or vasodilators.)
INOCOR lactate injection is indicated for the short-term management of cor
tive heart failure. Because of limited experience and potential for serious adv
effects (see ADVERSE REACTIONS), INOCOR should be used only in patients whc
be closely monitored and who have not responded adequately to digitalis, diure
and/or vasodilators. Although most patients have been studied hemodynamical
periods only up to 24 hours, some patients were studied for longer periods
demonstrated consistent hemodynamic and clinical effects. The duration of the
should depend on patient responsiveness.
CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients
are hypersensitive to it.
It is also contraindicated in those patients known to be hypersensitive to bisul
PRECAUTIONS *General:* INOCOR lactate injection should not be used in patients
severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruc
Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrc
subaortic stenosis.
During intravenous therapy with INOCOR lactate injection, blood pressure
heart rate should be monitored and the rate of infusion slowed or stopped in pat
showing excessive decreases in blood pressure.
Patients who have received vigorous diuretic therapy may have insuffi
cardiac filling pressure to respond adequately to INOCOR lactate injection, in v
case cautious liberalization of fluid and electrolyte intake may be indicated.
Supraventricular and ventricular arrhythmias have been observed in the
high-risk population treated. While amrinone per se has not been shown t
arrhythmogenic, the potential for arrhythmia, present in congestive heart failure i
may be increased by any drug or combination of drugs.
Thrombocytopenia and hepatotoxicity have been noted (see ADVE
REACTIONS).
LABORATORY TESTS *Fluid and electrolytes*: Fluid and electrolyte changes and
function should be carefully monitored during amrinone lactate therapy. Improve
in cardiac output with resultant diuresis may necessitate a reduction in the do
diuretic. Potassium loss due to excessive diuresis may predispose digitalized pat
to arrhythmias. Therefore, hypokalemia should be corrected by potassium su
mentation in advance of or during amrinone use.
DRUG INTERACTIONS In a relatively limited experience, no untoward clinical r
festations have been observed in patients in whom INOCOR lactate injection was
concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, n
prolol, propranolol, hydralazine, prazosin, isosorbide dinitrate, nitroglycerine; chlor
done, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, capt
heparin, warfarin, potassium supplements, insulin, diazepam.
One case of excessive hypotension was reported when amrinone was
concurrently with disopyramide.
Until additional experience is available, concurrent administration with Norp
disopyramide should be undertaken with caution.
USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for u
acute myocardial infarction.
USE IN CHILDREN Safety and effectiveness in children have not been establishe
USE IN PREGNANCY *Pregnancy category C:* In New Zealand white rabbits, amri
has been shown to reduce fetal skeletal and gross external malformations at oral d
of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr ra
using oral doses up to 32 mg/kg/day did not confirm this finding. No malforma
were seen in rats receiving amrinone intravenously at the maximum dose u
15 mg/kg/day (approximately the recommended daily IV dose for patients with
gestive heart failure). There are no adequate and well-controlled studies in preg
women. Amrinone should be used during pregnancy only if the potential be
justifies the potential risk to the fetus.
USE IN NURSING MOTHERS Caution should be exercised when amrino
administered to nursing women, since it is not known whether it is excreted in hu
milk.
ADVERSE REACTIONS *Thrombocytopenia*: Intravenous INOCOR lactate inje
resulted in platelet count reductions to below 100,000/mm^3 in 2.4% of patients.
Gastrointestinal effects: Gastrointestinal adverse reactions reported with INO
lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdor
pain (0.4%), and anorexia (0.4%).
Cardiovascular effects: Cardiovascular adverse reactions reported with INO
lactate injection include arrhythmia (3%) and hypotension (1.3%).
Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg
amrinone showed dose-related hepatotoxicity manifested either as enzyme elev
or hepatic cell necrosis or both. Hepatotoxicity has been observed in man follo
long-term oral dosing and has been observed, in a limited experience (0.2%), follo
IV administration of amrinone.
Hypersensitivity: There have been reports of several apparent hypersensitivity
tions in patients treated with oral amrinone for about two weeks. Signs and symp
were variable but included pericarditis, pleuritis, and ascites (one case); myositis
interstitial shadowing on chest x-ray and elevated sedimentation rate (one case)
vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case)
first patient died, not necessarily of the possible reaction, while the last two reso
with discontinuation of therapy. None of the cases were rechallenged, so attribut
amrinone is not certain, but possible hypersensitivity reactions should be conside
any patient maintained for a prolonged period on amrinone.
General. Additional adverse reactions observed in intravenous amrinone cl
studies include fever (0.9%), chest pain (0.2%), and burning at the site of inje
(0.2%).
OVERDOSAGE Doses of INOCOR lactate injection may produce hypoter
because of its vasodilator effect. If this occurs, amrinone administration shoul
reduced or discontinued. No specific antidote is known, but general measure
circulatory support should be taken.
MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions*: Asyn
matic platelet count reduction (to less than 150,000/mm^3) may be reversed withir
week of a decrease in drug dosage. Further, with no change in drug dosage, the c
may stabilize at lower than predrug levels without any clinical sequelae. Predrug pla
counts and frequent platelet counts during therapy are recommended to ass
decisions regarding dosage modifications
Should a platelet count less than 150,000/mm^3 occur, the following actions ma
considered:
- Maintain total daily dose unchanged, since in some cases counts have e
stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceed
potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequ
with IV therapy, should severe or debilitating ones occur, the physician may wi
reduce dosage or discontinue the drug based on the usual benefit-to
considerations.
Hepatic toxicity: In clinical experience to date with IV administration, hepatotoxicit
rarely been observed. If acute marked alterations in liver enzymes occur togethe
clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amri
therapy should be promptly discontinued.
If less than marked enzyme alterations occur without clinical symptoms, t
nonspecific changes should be evaluated on an individual basis. The clinician
wish to continue amrinone and reduce the dosage or discontinue the drug base
the usual benefit-to-risk considerations
HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containing INO
5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR la
equivalent to 5-mg base and 0.25 mg sodium metabisulfite in water for injection.



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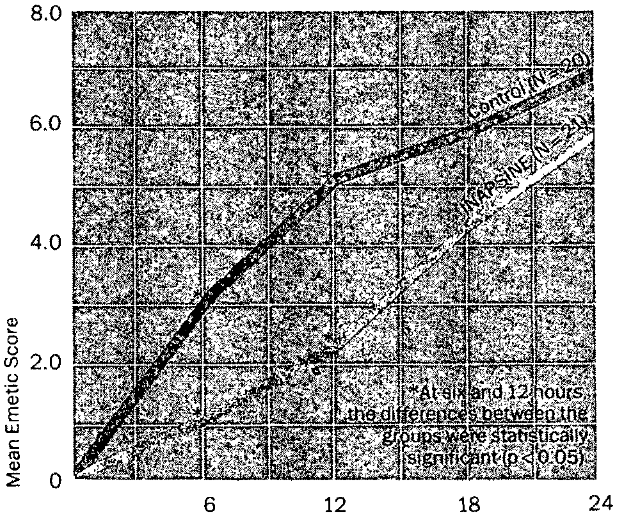
1974:

“. . . we found droperidol [INAPSINE®] to be a safe and effective prophylactic antiemetic agent in this group of patients at high emetic risk.” ①

Double-blind study of 41 patients undergoing hysterectomy. Twenty-one patients received 5 mg INAPSINE shortly after surgery began, while 20 patients received placebo. Postoperative emesis was rated according to an emetic scoring system. Patients receiving INAPSINE had significantly less frequent and less severe nausea, retching and vomiting during the first 12 postoperative hours.

INAPSINE vs placebo: mean total emetic scores. The lower the score, the fewer and less severe the incidents of emesis. (Adapted from Patton CM Jr, Moon MR, Dannemiller FJ¹)

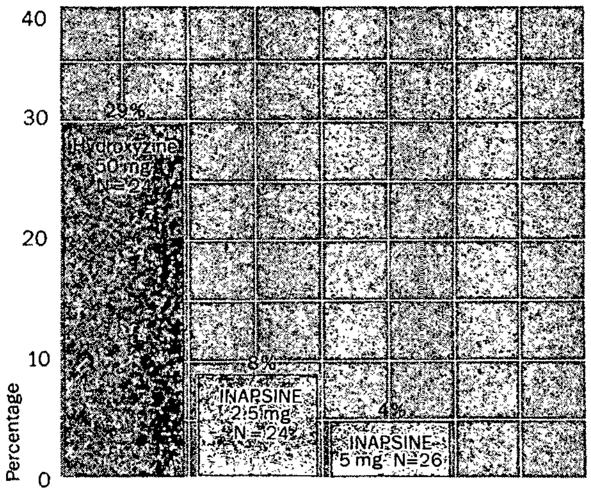


1984:

“The incidence of postoperative nausea/vomiting . . . was higher in patients who received hydroxyzine as premedicant, compared to those who received droperidol [INAPSINE] ($p < 0.05$).” ②

Double-blind comparison of INAPSINE 5 mg, INAPSINE 2.5 mg and hydroxyzine 50 mg, combined with meperidine or morphine and glycopyrrolate, as premedication in 74 women undergoing major elective gynecologic surgery. Significantly fewer of the patients receiving INAPSINE experienced postoperative nausea/vomiting than those receiving hydroxyzine ($p < 0.05$).

Percentage of patients experiencing postoperative nausea/vomiting according to premedication ($p < 0.05$). (Based on Mehta P, Theriot E, Mehrotra D, et al²)



Before prescribing please consult complete prescribing information, of which the following is a brief summary.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.
Droperidol is a neuroleptic (tranquilizer) agent.

DESCRIPTION: *2 ml. and 5 ml. ampoules:* Each ml. contains Droperidol 2.5 mg. and lactic acid for pH adjustment to 3.4 ± 0.4
10 ml. vials: Each ml. contains Droperidol 2.5 mg. with 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4

INDICATIONS: INAPSINE (droperidol) is indicated: • to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; • for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia; • in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE.
As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be

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References:

① Patton CM Jr, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. *Anesth Analg* 1974;53:361-364.

② Mehta P, Theriot E, Mehrotra D, et al: Comparative evaluation of preanesthetic medications. *Cur Ther Res* 1984;35:715-720.

found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

ADVERSE REACTION: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and post-operative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur, if these remain untreated, respiratory arrest could occur.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

If INNOVAR® injection is administered in addition to INAF (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contai in the INNOVAR injection. See INNOVAR injection Package I for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedure
Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 30 to 60 minutes before the procedure. Additional 1.25 to mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may b administered, usually intravenously (see warning regardin with concomitant narcotic analgesic medication and the p bility of widely differing durations of action).
Note: When INAPSINE (droperidol) is used in certain pro dures, such as bronchoscopy, appropriate topical anesthe still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) m be administered intramuscularly or slowly intravenously w additional sedation is required.

How Supplied: *2 ml. and 5 ml. ampoules*—packages of 10; *10 ml. multiple-dose vials*—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10
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The importance of brain monitoring is determined by which end of the scalpel you're on.

Consider this scene.

It is near the completion of a delicate surgery. The vital signs are normal. To all outward appearances, the operation will be a success.

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The moment it senses a brain abnormality, it signals the surgical team so that the difficulty can be corrected in time.

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And, in the process, it is bound to affect the very definition of "acceptable risk."

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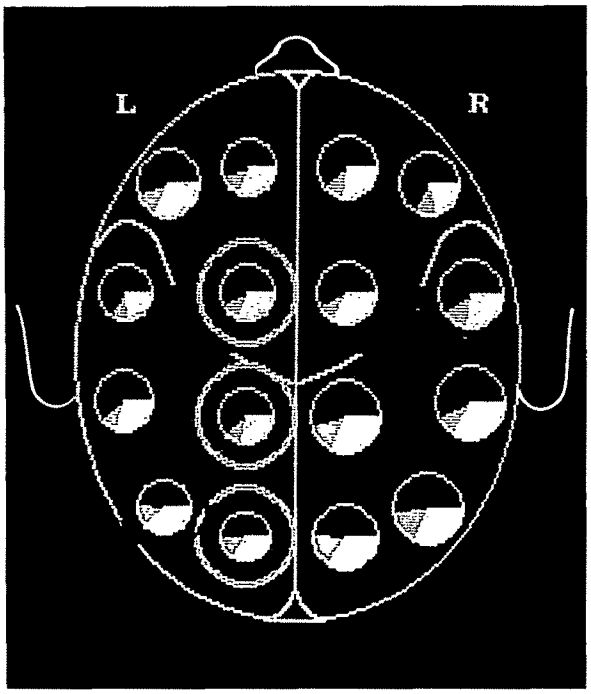
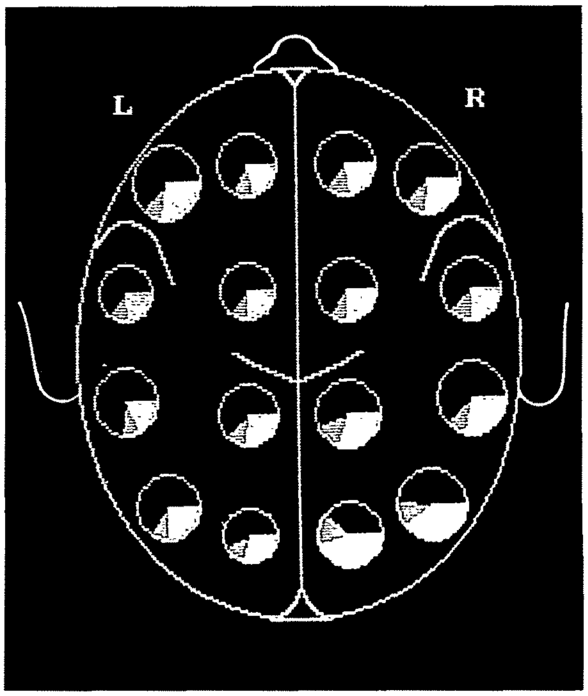
CNS

Brain (EEG) Monitoring can Reduce the Risk

Case: 84 year old physician with history of hypertension

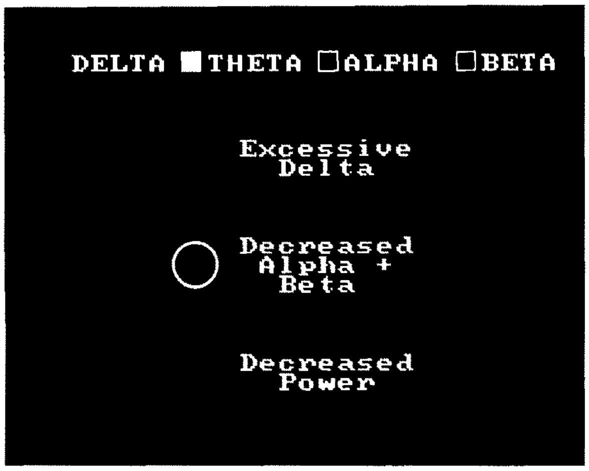




Procedure: Left Carotid Endarterectomy

Problem: Focal Ischemia developing a few minutes after clamping (BP 140/70).

Resolution: Blood pressure was increased to 160/80. No shunt was required.



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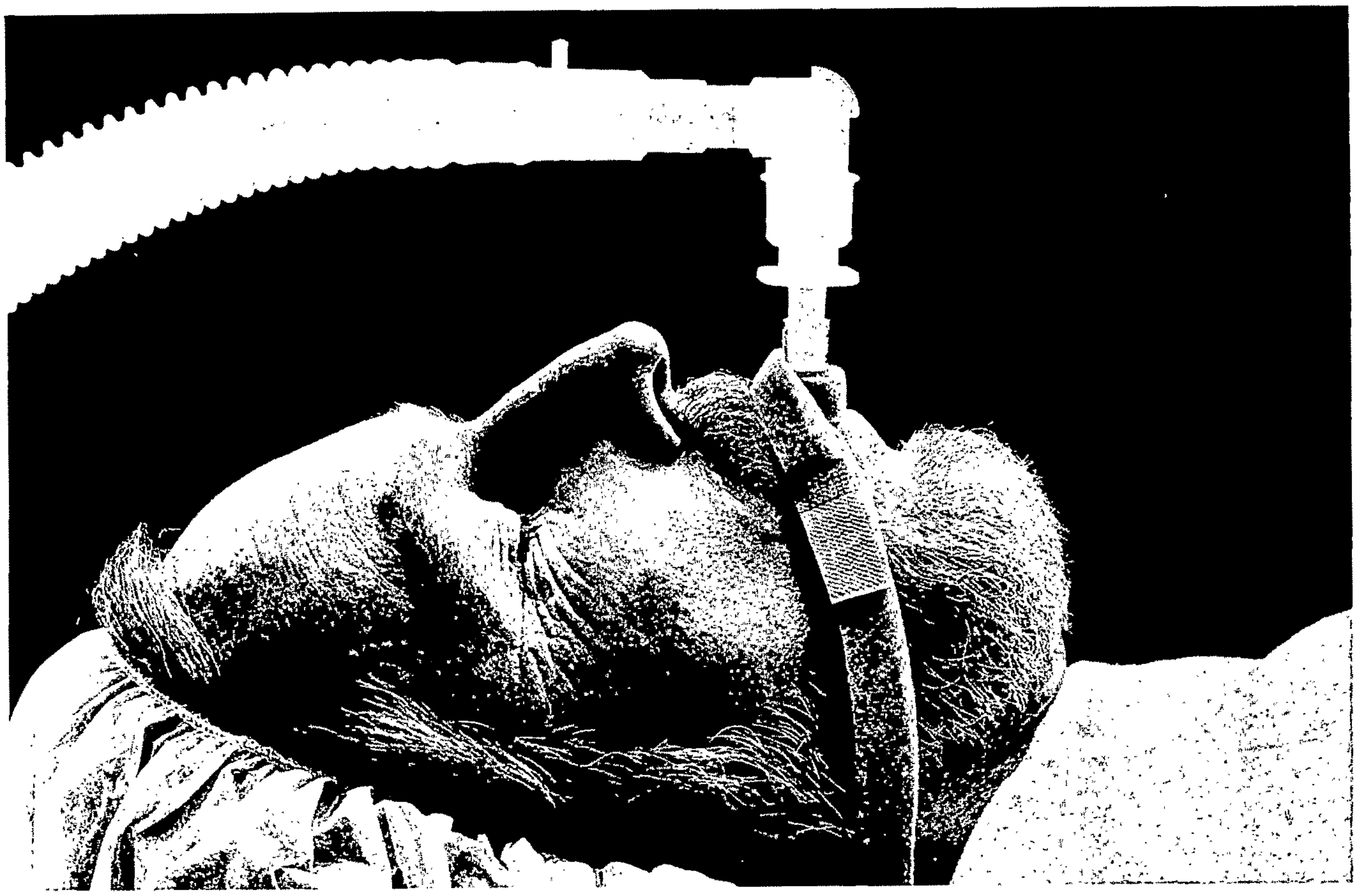

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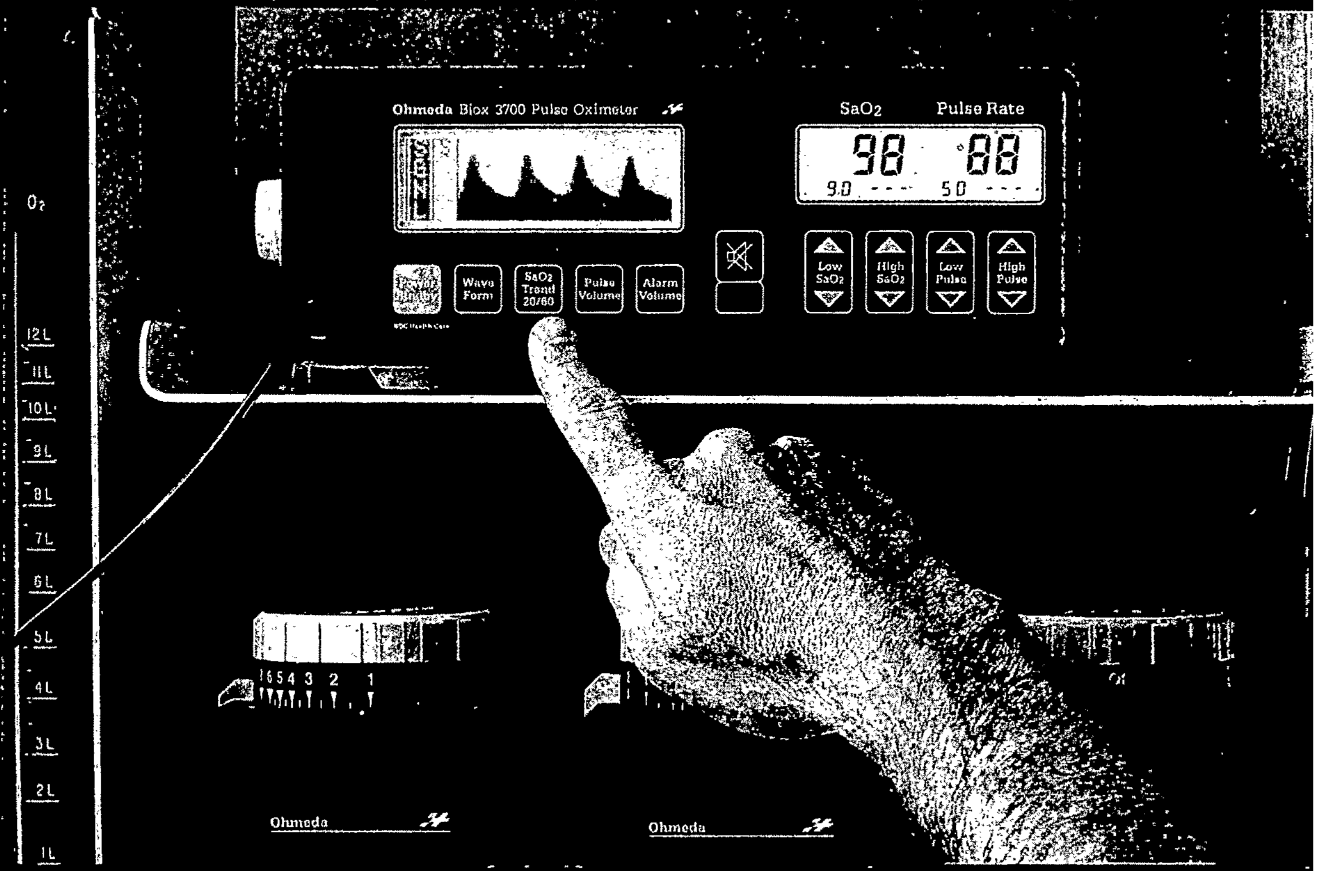

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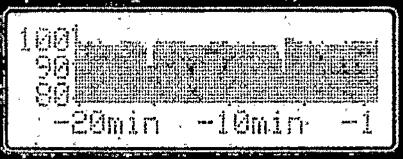

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Comparison of Sufentanil and Enflurane–Nitrous Oxide Anesthesia for Myocardial Revascularization

Paul N. Samuelson, MD, J. G. Reves, MD, James K. Kirklin, MD, Edwin Bradley Jr, PhD, Kathleen D. Wilson, CRNA, and Mary Adams, BS

SAMUELSON PN, REVES JG, KIRKLIN JK, BRADLEY E Jr, WILSON KD, ADAMS M. Comparison of sufentanil and enflurane–nitrous oxide anesthesia for myocardial revascularization. Anesth Analg 1986;65:217–26.

This study compared the stress response in patients with coronary artery disease undergoing myocardial revascularization anesthetized with either sufentanil and oxygen or enflurane–nitrous oxide and oxygen. Throughout induction and maintenance of anesthesia, and while the patients were in the intensive care unit, hemodynamics plus plasma catecholamine, sufentanil, and enflurane concentrations were recorded and compared. Three groups were studied: sufentanil, 15 μg/kg at induction; sufentanil, 15 μg/kg at induction plus 10 μg/kg on initiation of cardiopulmonary bypass (CPB); and enflurane anesthesia. Hemodynamics were remarkably stable in all groups but required considerable fine tuning when enflurane was administered. The "stress" of CPB was blunted by the additional dose of sufentanil, as well as by enflurane. This was reflected in those patients receiving the extra sufentanil or enflurane by less severe increases in their epinephrine or norepinephrine concentrations and by less frequent use of sodium nitroprusside to control mean arterial pressure compared to the group of patients given the lower-dose sufentanil. This study suggests that higher blood levels of sufentanil can attenuate, but not eliminate, the stress response to CPB, as can enflurane, and that both the narcotic and inhalation anesthetic techniques for patients with coronary artery disease were quite satisfactory.

Key Words: ANESTHETICS, INTRAVENOUS—sufentanil. ANALGESICS—sufentanil. ANESTHESIA—cardiovascular. ANESTHETICS, VOLATILE—enflurane.

Sufentanil is a synthetic narcotic 5–10 times as potent as fentanyl in humans (1) that has been used in large doses (15–25 μg/kg) to produce surgical anesthesia in patients undergoing coronary artery surgery (2,3). These studies have documented minimal hemodynamic alterations. An unproven hypothesis concerning opioids is that the more potent the narcotic analgesic, the more opioid receptor-specific the drug and the fewer the side effects (4). Considering this hypothesis, the very potent opioid, sufentanil, should block the so-called "stress responses" during anesthetic induction and surgical procedures. The purpose of this study was to evaluate the effectiveness of sufentanil in blocking the stress response to surgery and cardiopulmonary bypass by comparing the hemodynamic and catecholamine responses in patients undergoing myocardial revascularization surgery anesthetized with either sufentanil–oxygen anesthesia or enflurane–nitrous oxide–oxygen anesthesia.

Methods

Forty-five patients scheduled for elective myocardial revascularization were studied. The study was approved by the Institutional Review Board, and informed consent was obtained from all patients. The patients were randomly assigned from a table of random numbers to receive either sufentanil or enflurane anesthesia. After the first 19 patients (ten sufentanil and nine enflurane) were studied, it became apparent that because of hypertension during cardiopulmonary bypass (CPB), an additional dose of sufentanil at the time of initiation of CPB was indicated. Thus the study included three groups of patients: ten patients (group 1) in whom anesthesia was induced with sufentanil, 15 μg/kg, and who were then ventilated with oxygen throughout the procedure; 14 patients (group 2) in whom anesthesia was induced with sufentanil, 15μg/kg, who also received an additional

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Received from the Departments of Anesthesiology and Surgery, The University of Alabama Medical Center, Birmingham, Alabama. Accepted for publication September 24, 1985.

Address correspondence to Dr. Samuelson, Department of Anesthesiology, The University of Alabama at Birmingham, University Station, Birmingham, AL 35294.

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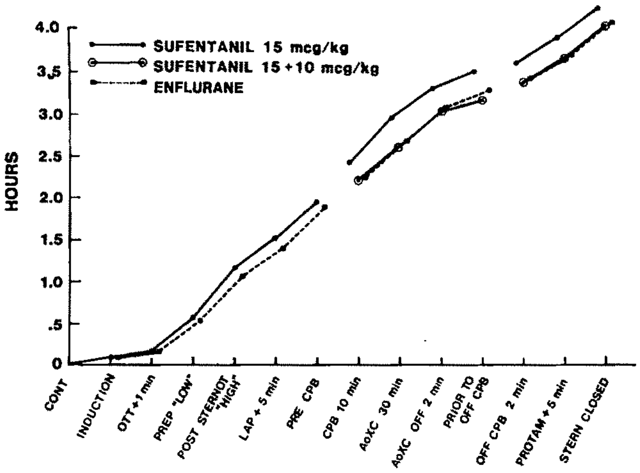

Figure 1. Measurement period vs real time duration. CONT, control/baseline; INDUCTION, induction; OTT + 1 min, 1 min after orotracheal intubation; PREP "LOW", lowest systolic pressure during prepping; POST STERNOT "HIGH", highest systolic blood pressure after sternotomy; LAP + 5 min, 5 min after left atrial line placement; PRE CPB, preceding cardiopulmonary bypass; CPB 10 min, 10 min into cardiopulmonary bypass; AoXC 30 min, 30 min after the aortic cross-clamp was placed; AoXC OFF 2 min, 2 min after the aortic cross-clamp was removed; PRIOR TO OFF CPB, immediately prior to coming off cardiopulmonary bypass; OFF CPB 2 min, 2 min after coming off cardiopulmonary bypass; PROTAM + 5 min, 5 min after protamine administration; STERN CLOSED, at sternal closure. No significant difference was found between groups.

supplement of 10 μg/kg of sufentanil at the initiation of CPB; and 21 patients (group 3) in whom anesthesia was induced with diazepam, 0.5 mg/kg, and anesthesia then maintained with enflurane and 50% nitrous oxide in oxygen. Group 3 patients received no opioids during the operation.

Premedication of all patients consisted of diazepam, 0.1–0.15 mg/kg orally; morphine, 0.1 mg/kg intramuscularly; and scopolamine, 0.4–0.5 mg intramuscularly given 90–120 min prior to anesthetic induction. Catheters were placed in two peripheral veins, in the radial artery, and in the pulmonary artery via the right internal jugular vein (Edwards–Swan–Ganz triple lumen thermodilution catheter). After control measurements, anesthesia was induced with intravenous sufentanil at a rate of 200–400 μg/min to a total of 15 μg/kg. Concomitantly, pancuronium, 0.1 mg/kg, was administered. In patients given enflurane (group 3), anesthesia was induced with diazepam, 0.5 mg/kg; pancuronium, 0.1 mg/kg; and 50% N_2O and oxygen plus enflurane (inspired concentration 1–2%). The following were measured serially: electrocardiogram (leads II and V_5); heart rate (HR) and rhythm; systemic arterial pressure (systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP)); mean right atrial pressure (RAP); pulmonary artery pressure (PAP) (systolic (SPAP) and diastolic (DPAP)); mean pulmonary artery occluded pressure (PAO); cardiac output (CO) (duplicate thermodilution); arterial blood gas tensions; arterial plasma concentrations of sufentanil or enflurane; plus norepinephrine and epinephrine concentrations. Hemodynamic measurements were made at end-expiration. Derived data consisted of the cardiac index (CI), stroke index (SI), heart rate systolic blood pressure product (RPP), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR). The formulae used for these derived data have been previously reported (5).

The bubble oxygenator was primed with 1000 ml Normosol®, 500 ml D_5 ½ NS, and 200 ml 25% albumin, and volume "additions" on CPB based on a minimum calculated machine–patient packed cell volume (PCV) ≥ 25%. Proximal anastomoses were placed before CPB with a side biting aortic clamp, if tolerated hemodynamically. Cardiopulmonary bypass was then established using a single venous cannula. All distal anastomoses were constructed during a single period of aortic occlusion, utilizing cold (4–6°C), crystalloid, potassium (30 mEq/L) cardioplegic solution for myocardial protection. The perfusate temperature was 28°C during most of the ischemic period, and myocardial cooling was further enhanced by continuous topical cooling with cold Ringer's lactate solution. Patients were rewarmed to 37°C (nasopharyngeal) before weaning from CPB.

Table 1. Adjuvant Treatment Protocol

Before CPB	SBP > 30% control: Sufentanil, 50 μg, then sodium nitroprusside, 200 μg/ml Enflurane ≤ 2% inspired, then sodium nitroprusside, 200 μg/ml SBP < 30% Control: Neosynephrine
During CPB	MAP > 80: Sufentanil, 50 μg, then sodium nitroprusside, 200 μg/ml Enflurane ≤ 3%, then sodium nitroprusside, 200 μg/ml
After CBP	MAP > 80: Sufentanil, 50 μg, N_2O 50%, then SNP Enflurane ≤ 2%, then SNP
CICU	MAP > 80 (with LAP 8–10, HR 90): Sodium nitroprusside, 200 μg/ml, by computer controlled closed-loop infusion

Abbreviations: CPB, cardiopulmonary bypass; SBP, systolic blood pressure (mm Hg); MAP, mean arterial blood pressure (mm Hg); LAP, left atrial pressure (mm Hg); HR, heart rate (beats/min); CICU, cardiac intensive care unit.

Table 2. Demographic Data[a]

	Group 1[b]	Group 2[b]	Group 3[b]
Number	10	14	21
Male/female	10/0	12/2	20/1
Age (yr)	56 ± 2.1	54 ± 2.2	55 ± 1.1
Weight (kg)	84 ± 3.0	86 ± 4.0	83 ± 2.8
Body surface area (m^2)	2.04 ± 0.042	2.06 ± 0.056	2.04 ± 0.039
History:			
Prior MI	8	11	13
Prior CHF	3	5	1
Left main	0	2	3
Drugs Pre-op:			
β-Blocker	10	8	17
TNG	10	14	19
Ca^{++} Blocker	0	7	7
Digoxin	2	3	1
Antihypertensives	0	0	2
Number of grafts	3.9 ± 0.41	4.7 ± 0.22	4.7 ± 0.23
AoXC time (min)	54 ± 5.4	52 ± 3.1	54 ± 2.8
CPB time (min)	79 ± 9.0	72 ± 5.6	79 ± 3.8

[a] Mean ± SEM. No significant differences between groups.

[b] Group 1, nonsupplemented sufentanil group; group 2, supplemented sufentanil group; group 3, enflurane group.

Abbreviations: CPB, cardiopulmonary bypass; AoXC, aortic cross clamp.

Table 3. Incidence of Adjuvant Treatment[a]

	Group(s)	(*n*)	Sodium nitroprusside	Neosynephrine	Other
Induction	1,2	24	0	1	0
	3	21	1	1	0
Prior to CPB	1,2	24	13	5	2 Atropine
	3	21	10	8	0
On CPB	1	10	$10^{b,c}$	0^{b}	0
	2	14	9	7	0
	3	21	7	5	0
After CPB	1	10	7	1	2 $CaCl_2$
	2	14	10	6^{d}	1 $CaCl_2$
	3	21	17	1	1 $CaCl_2$

[a] Data is expressed as number of patients treated.

[b] $P < 0.05$, group 1 vs group 2.

[c] $P < 0.05$, group 1 vs group 3.

[d] $P < 0.05$, group 2 vs group 3.

Abbreviations: CPB, cardiopulmonary bypass; Group 1, unsupplemented sufentanil group; group 2, supplemented sufentanil group; group 3, enflurane group.

Control measurements were made with the patient resting comfortably in the operating room while breathing oxygen for at least 5 min until hemodynamics were stable (±10% of consecutive observations). Additional measurements were made 1) with loss of consciousness (defined as failure to respond to verbal commands and loss of eyelash reflex); 2) 1 min after orotracheal intubation; 3) at the time of the lowest systolic pressure during preparation for surgery; 4) at the time of the highest systolic blood pressure after sternotomy (or 2 min after sternotomy if no peak was noted); 5) 5 min after left atrial line placement; 6) immediately preceding CPB; 7) 10 min after initiation of CPB; 8) 30 min after the aortic cross-clamp was placed; 9) two min after the aortic cross-clamp was removed; 10) immediately prior to discontinuation of CPB; 11) 2 min after discontinuation of CPB; 12) 5 min after protamine administration; 13) during sternal closure; and 14) upon admission to the cardiac intensive care unit (CICU). These measurement periods are plotted vs the real time duration in Figure 1.

From admission to the CICU until 6:00 AM the first postoperative day, the mean arterial pressure was kept at 80 mm Hg utilizing our computer-controlled closed-loop sodium nitroprusside infusion system (6); amounts and rates of nitroprusside administered were recorded. Chest drainage and urine output were quan-

Table 4. Hemodynamic Data for Combined Groups

Measurement period and group(s)	HR	SBP	DBP	MAP	RAP	SPAP	DPAP	PAO or LAP	RPP	CI	SI	SVR	PVR
Control													
1,2	62 ± 3.1	137 ± 4.2	65 ± 1.7	89 ± 2.4	7 ± 0.7	30 ± 1.4^{b}	10 ± 0.9	13 ± 0.9	8.5 ± 0.54	2.6 ± 0.21	43 ± 2.5	1332 ± 72.2	68 ± 9.3
3	60 ± 2.6	136 ± 3.7	69 ± 1.6	91 ± 2.1	7 ± 0.7	25 ± 1.6	9 ± 1.0	11 ± 0.8	8.2 ± 0.42	2.5 ± 0.17	43 ± 2.8	1442 ± 98.4	56 ± 8.7
Induction													
1,2	70 ± 2.3^{a}	123 ± 5.4^{a}	64 ± 2.7	84 ± 3.5	8 ± 0.7	26 ± 1.2^{a}	12 ± 0.9	12 ± 0.9	8.7 ± 0.51	2.9 ± 0.23	41 ± 2.8	1105 ± 53.6^{a}	77 ± 10.0
3	74 ± 2.6^{a}	119 ± 4.1^{a}	65 ± 2.4	83 ± 2.9^{a}	7 ± 0.6	24 ± 1.7	10 ± 1.0	10 ± 0.9	8.9 ± 0.47	2.6 ± 0.14	35 ± 1.4^{a}	1236 ± 73.6	64 ± 6.2
OTT + 1 min													
1,2	72 ± 2.8^{a,b}	126 ± 4.7^{a}	65 ± 2.6^{b}	85 ± 3.2	7 ± 0.6	27 ± 1.3	12 ± 0.9	12 ± 0.9	9.1 ± 0.55^{b}	2.8 ± 0.22	40 ± 2.8	1140 ± 54.3^{a}	82 ± 11.6
3	83 ± 3.0^{a}	136 ± 5.0	74 ± 2.5	95 ± 3.3	6 ± 0.8	26 ± 1.6	12 ± 1.1^{a}	11 ± 1.0	11.3 ± 0.58^{a}	2.8 ± 0.22	34 ± 2.1^{a}	1317 ± 76.7	76 ± 9.3
Prep "Low"													
1,2	62 ± 2.4^{b}	112 ± 4.0^{a}	59 ± 2.3^{a}	77 ± 2.8^{a}	6 ± 0.8^{a}	23 ± 1.2^{a}	8 ± 0.9^{a}	8 ± 0.9^{a}	7.0 ± 0.38^{a}	2.2 ± 0.15^{a}	35 ± 2.6^{a}	1379 ± 63.1	109 ± 12.6
3	71 ± 2.6^{a}	114 ± 4.5^{a}	66 ± 3.1	82 ± 3.5^{a}	6 ± 0.8	23 ± 1.3^{a}	10 ± 1.0	10 ± 1.0	8.1 ± 0.46	2.0 ± 0.09^{a}	29 ± 1.2^{a}	1560 ± 77.0	91 ± 10.6^{a}
Post-Stern "High"													
1,2	62 ± 2.6^{b}	147 ± 5.0^{a}	76 ± 3.1^{a,b}	100 ± 3.6^{a,b}	6 ± 0.7^{a}	25 ± 0.9^{a}	10 ± 0.8	10 ± 0.9^{a}	9.2 ± 0.53^{b}	2.1 ± 0.18^{a}	35 ± 2.8^{a,b}	1900 ± 121.4^{a,b}	100 ± 10.6
3	74 ± 2.3^{a}	158 ± 4.5^{a}	90 ± 2.2^{a}	113 ± 2.8^{a}	4 ± 0.7^{a}	23 ± 1.4	9 ± 1.1	9 ± 1.0^{a}	11.7 ± 0.51^{a}	1.9 ± 0.13^{a}	26 ± 1.8^{a}	2494 ± 213.9^{a}	109 ± 12.3^{a}
LAP + 5 min													
1,2	74 ± 2.7^{a}	126 ± 4.4^{a}	65 ± 2.5	85 ± 3.0	5 ± 0.6^{a}	24 ± 1.1^{a,b}	7 ± 0.8^{a}	8 ± 0.9^{a}	9.3 ± 0.45	2.3 ± 0.18	32 ± 2.2^{a}	1482 ± 110.1	105 ± 15.3
3	75 ± 2.6^{a}	120 ± 3.9^{a}	68 ± 2.4	85 ± 2.7	4 ± 0.6^{a}	20 ± 0.9^{a}	6 ± 0.7^{a}	6 ± 0.7^{a}	9.0 ± 0.44	2.0 ± 0.11^{a}	27 ± 1.7^{a}	1697 ± 116.2	99 ± 8.1^{a}
Pre-CPB													
1,2	77 ± 2.6^{a}	124 ± 3.4^{a}	66 ± 2.4	85 ± 2.5	5 ± 0.6^{a}	22 ± 1.0^{a}	6 ± 0.8^{a}	7 ± 0.7^{a}	9.5 ± 0.40^{a}	2.1 ± 0.15^{a}	28 ± 1.8^{a}	1599 ± 109.5^{a}	102 ± 11.6
3	73 ± 2.9^{a}	122 ± 2.6^{a}	67 ± 1.7	85 ± 1.8	4 ± 0.8^{a}	21 ± 1.2^{a}	6 ± 1.0^{a}	5 ± 0.9^{a}	8.9 ± 0.46	1.8 ± 0.13^{a}	25 ± 1.2^{a}	1882 ± 136.3^{a}	147 ± 24.2^{a}
On CPB + 10 min													
1				73 ± 5.5^{a,c,e}						1.8 ± 0.06^{a}		1539 ± 107.7^{c,e}	
2				44 ± 3.3^{a}						1.8 ± 0.03^{a}		890 ± 85.2^{a}	
3				50 ± 3.2^{a}						1.9 ± 0.02^{a}		1041 ± 75.8^{a}	
AoXC + 30 min													
1				80 ± 2.5						1.6 ± 0.09^{a,c,e}		2058 ± 145.6^{a,c,e}	
2				68 ± 4.9^{a}						1.8 ± 0.04^{a}		1366 ± 107.2	
3				71 ± 2.3^{a}						1.8 ± 0.03^{a}		1536 ± 65.9	

AoXC off 2 min													
1				75 ± 4.0^{a,c,e}						1.9 ± 0.04^{a}		1514 ± 66.3^{c,e}	
2				64 ± 4.1^{a}						1.9 ± 0.05^{a}		1214 ± 88.1	
3				59 ± 3.4^{a}						2.0 ± 0.03^{a}		1145 ± 64.6^{a}	
Prior to off CPB													
1				70 ± 5.0^{a}						1.9 ± 0.04^{a}		1407 ± 90.2	
2				67 ± 4.5^{a,d}						1.9 ± 0.05^{a}		1258 ± 92.8	
3				80 ± 3.7^{a}						2.0 ± 0.03^{a}		1478 ± 72.2	
Off CPB + 2 min													
1	89 ± 2.5^{a}	109 ± 5.7^{a}	64 ± 3.2	79 ± 4.0^{a}	5 ± 1.1	24 ± 1.5^{e}	10 ± 1.2	9 ± 1.0^{a}	9.6 ± 0.42^{a}	2.5 ± 0.17^{e}	29 ± 2.3^{a}	1196 ± 113.7^{e}	82 ± 13.6
2	92 ± 1.9^{a}	102 ± 4.6^{a}	56 ± 3.0^{a,d}	72 ± 3.3^{a,d}	7 ± 1.3	29 ± 1.1	10 ± 1.1	11 ± 0.8	9.3 ± 0.39	3.2 ± 0.18	34 ± 1.8^{a}	807 ± 54.2^{a,d}	64 ± 13.0
3	90 ± 2.2^{a}	113 ± 4.5^{a}	66 ± 2.2	82 ± 2.8^{a}	6 ± 0.7	26 ± 0.9	8 ± 0.8	10 ± 0.8	10.2 ± 0.38^{a}	2.9 ± 0.14^{a}	32 ± 1.8^{a}	1081 ± 69.0^{a}	63 ± 7.2
Protamine + 5 min													
1	92 ± 2.4^{a}	112 ± 4.3^{a}	63 ± 3.8	80 ± 3.9^{a}	3 ± 0.8^{a}	24 ± 2.2	10 ± 1.5^{c}	9 ± 1.2^{a}	10.3 ± 0.46^{a}	2.3 ± 0.15^{c,e}	25 ± 1.8^{a}	1373 ± 131.8^{c,e}	90 ± 23.4^{a}
2	88 ± 2.8^{a}	112 ± 3.0^{a}	58 ± 2.6^{d}	76 ± 2.3^{a}	5 ± 0.8^{a}	26 ± 1.9^{a,d}	9 ± 1.0^{d}	10 ± 0.8^{a,d}	9.9 ± 0.44	3.0 ± 0.16	34 ± 1.7	946 ± 53.3^{a}	71 ± 9.4
3	90 ± 1.4^{a}	116 ± 2.4^{a}	65 ± 2.1	82 ± 1.8^{a}	4 ± 0.4^{a}	22 ± 0.9^{a}	6 ± 0.4^{a}	7 ± 0.4^{a}	10.4 ± 0.28^{a}	2.8 ± 0.12	31 ± 1.3^{a}	1141 ± 48.9^{a}	58 ± 8.9
Sternum Closed													
1	88 ± 2.8^{a}	116 ± 2.7^{a}	66 ± 2.1	82 ± 2.2	5 ± 1.0	23 ± 1.3^{a}	9 ± 1.1	9 ± 0.8^{a}	10.2 ± 0.40^{a}	2.0 ± 0.16^{e}	23 ± 1.8^{a,c}	1562 ± 103.4^{c}	90 ± 24.5^{a}
2	92 ± 2.7^{a}	120 ± 3.1^{a}	65 ± 3.1	83 ± 2.6	6 ± 0.8	25 ± 1.6^{a,d}	10 ± 1.0^{d}	9 ± 0.8^{a}	11.0 ± 0.46^{a}	2.5 ± 0.16	27 ± 1.5^{a}	1290 ± 91.2	96 ± 12.3
3	88 ± 1.5^{a}	119 ± 11.4^{a}	68 ± 2.1	85 ± 1.9	5 ± 0.5^{a}	21 ± 0.8^{a}	7 ± 0.4^{a}	8 ± 0.4^{a}	10.5 ± 0.24^{a}	2.6 ± 0.16	30 ± 1.7^{a}	1285 ± 78.2	68 ± 7.4
CICU Admission	94 ± 4.8^{a}												
1	91 ± 1.6^{a}	124 ± 8.8^{a,c}	65 ± 3.2^{c}	87 ± 4.9^{c}	9 ± 1.2^{a}			12 ± 1.5^{c}	11.6 ± 7.99^{a,c}	2.1 ± 0.22^{c}	22 ± 2.6^{a,c}	1481 ± 101.2	
2	96 ± 2.2^{a}	120 ± 4.2^{a,d}	66 ± 2.3^{d}	85 ± 2.8^{d}	7 ± 0.9			9 ± 1.0	10.9 ± 3.57^{a,d}	2.5 ± 0.10	27 ± 0.9^{a}	1239 ± 67.1	
3		148 ± 3.9^{a}	80 ± 2.0^{a}	104 ± 2.6^{a}	7 ± 0.4			8 ± 0.5^{a}	14.2 ± 5.19^{a}	3.0 ± 0.18^{a}	31 ± 1.9^{a}	1413 ± 117.5	

Abbreviations: HR, heart rate (beats/min); SBP, DBP, MAP, systolic, diastolic, mean arterial blood pressure (mm Hg), respectively; RAP, right atrial pressure (mm Hg); SPAP, DPAP, systolic, diastolic pulmonary artery pressure (mm Hg), respectively; PAO, pulmonary artery occluded pressure (mm Hg); LAP, left atrial pressure (mm Hg); RPP, rate pressure product (torr·beats/min·10^3); CI, cardiac index (L/min/m^2); SI, stroke index (ml / min / m^2); SVR, PVR, systemic and pulmonary vascular resistance (dynes·sec·cm^{-5}), respectively.

See text for details about Control, Induction, and other measurement periods. Group 1, unsupplemented sufentanil group; group 2, supplemented sufentanil group; group 3, enflurane group.

[a] $P < 0.05$ $\bar{x}$ vs respective control. [b] $P < 0.05$ groups 1 and 2 (sufentanil) vs group 3 (enflurane). [c] $P < 0.05$ group 1 vs group 3. [d] $P < 0.05$ group 2 vs group 3. [e] $P < 0.05$ group 1 vs group 2.

titated using our computer patient management system. Heart rate, if less than 90 beats/min, was augmented with atrial pacing. Left atrial pressures were kept at approximately 8–10 mm Hg with infusion of crystalloid, 5% albumin, or blood.

An "adjuvant treatment protocol" was strictly defined and followed as listed in Table 1. The use of these drugs was qualitatively and quantitatively recorded for each of the measurement periods. All intravenous fluids were recorded; and cumulative fluid input, urine output, and chest drainage measurements were made throughout the study period.

Plasma sufentanil concentrations were measured utilizing the extraction method previously described by Gillespie et al. and a gas chromatograph mass spectrometer detection technique (7). Serum enflurane concentrations were measured with a gas chromatographic technique. Serum epinephrine and norepinephrine were determined by high-performance liquid chromatography with electrochemical detection by a modification of the method of Keller et al. (8).

Data are expressed as means plus or minus SEM. For analysis between groups a one-way analysis of variance was used. Analysis within groups was made by a repeated measures analysis of variance. Pairwise comparisons between means used the Fisher's protected least significance difference test (9,10). Differences were deemed significant if $P < 0.05$.

Results

There were no significant differences in the demographic characteristics of the groups (Table 2). There also were no significant differences in aortic cross-clamp times, durations of CPB, or numbers of distal saphenous vein graft anastomoses performed. Before CPB, the data in each sufentanil patient (groups 1 and 2, $n = 24$) were combined for purposes of analysis. According to the adjuvant treatment protocol for hemodynamic variation, this group of 24 received 0.7 ± 0.24 μg/kg additional sufentanil prior to CPB. The division of sufentanil patients occurred with initiation of CPB; ten patients (group 1) received minimal additional sufentanil (0.5 ± 0.21 μg/kg during CPB and 0.6 ± 0.30 μg/kg after CPB) and the sufentanil supplemented group (group 2) of 14 patients received 10.2 ± 0.15 μg/kg additional sufentanil during CPB and none after CPB.

Utilizing the adjuvant treatment protocol, many patients required treatment with a vasodilator (sodium nitroprusside) and vasoconstrictor (neosynephrine) before, during, and after CPB. Significantly more group 1 unsupplemented sufentanil patients required nitroprusside on CPB than group 2 supplemented sufentanil patients or group 3 enflurane-anesthetized patients. Significantly more group 2 patients required neosynephrine during CPB than group 1 patients and after CPB more neosynephrine than the enflurane group (group 3) (Table 3).

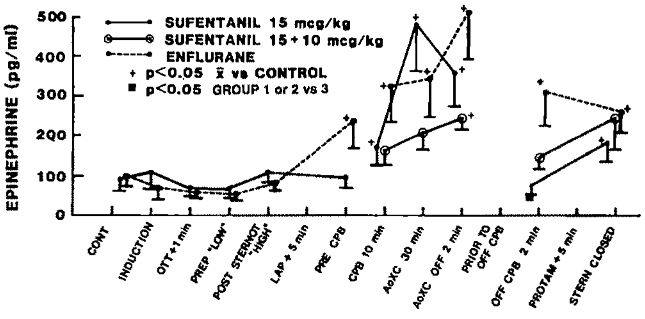

Figure 2. Epinephrine concentrations. Data plotted as mean ± SEM. See legend to Figure 1 for explanation of abbreviations.

The hemodynamic values are in Table 4. Statistically significant differences within and among the groups are indicated. Prior to CPB, there were few hemodynamic differences among groups. From intubation until sternotomy, heart rate was higher in the group 3 patients, and after sternotomy, the mean arterial blood pressure also was higher in group 3 patients. Thus the rate pressure product for the enflurane patients after intubation and sternotomy was higher than with sufentanil. Right atrial pressure, pulmonary artery occluded pressure, and pulmonary artery pressures were similar in all groups, decreasing gradually before initiating CPB. The cardiac index decreased slightly in all groups prior to CPB. The stroke index was significantly depressed in the enflurane group after sternotomy. Pulmonary vascular resistance increased similarly in all groups prior to CPB as did systemic vascular resistance, which was significantly higher only at the time of sternotomy in the enflurane group.

Cardiopulmonary bypass produced different responses in the three groups. There was a higher mean arterial pressure in the unsupplemented sufentanil patients (group 1) immediately after initiating CPB. There was no difference between patients given enflurane (group 3) and those given supplemental sufentanil (group 2). Mean blood pressure correlated with a significantly higher systemic vascular resistance in the group 1 patients. Immediately prior to discontinuation of CPB, the mean arterial pressure was significantly lower in the supplemented sufentanil patients (group 2) than in the enflurane patients (group 3).

After CPB, the systemic vascular resistance was

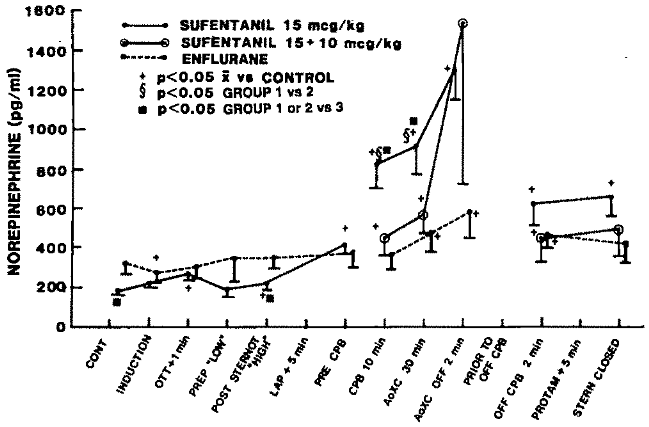

Figure 3. Norepinephrine concentrations. Data plotted as mean ± SEM. See legend to Figure 1 for explanation of abbreviations.

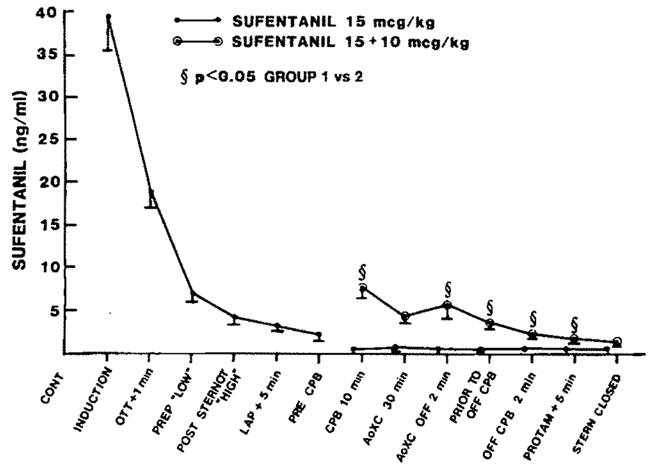

Figure 4. Plot of sufentanil concentrations (mean ± SEM) vs sample time for unsupplemented (Group 1) and supplemented (Group 2) sufentanil groups. See legend to Figure 1 for explanation of abbreviations.

initially lower in the supplemented sufentanil patients associated with a higher cardiac index, but the difference was not statistically significant. Cardiac index and stroke index were significantly lower in the unsupplemented sufentanil patients after CPB.

Upon admission to the CICU, the blood pressure was significantly lower in both groups 1 and 2 than in group 3. Cardiac index and stroke index remained significantly lower, despite an elevated left atrial pressure in the unsupplemented sufentanil group (group 1).

Serum epinephrine and norepinephrine concentrations are shown in Figures 2 and 3. Epinephrine remained at control values in all groups until just prior to CPB in the enflurane group (group 3) when it increased. Prior to CPB, norepinephrine remained near normal in all groups, but was lower at some points in both sufentanil groups. Norepinephrine concentrations were higher early during CPB in group 1 than in groups 2 or 3. Of note is the four- to five-fold increase in epinephrine during CPB in the enflurane and unsupplemented sufentanil group (groups 3 and 1), compared to only a two-fold increase in the supplemented sufentanil group (group 2). A statistically significant difference was noted between group 2 and group 3 immediately upon discontinuation of CPB. There was only about a two-fold increase in norepinephrine concentrations early in CPB in groups 2 and 3. From control to late in CPB, the norepinephrine concentrations increased five to seven times in both groups 1 and 2. However, the large standard error of the mean precluded a statistically significant difference with group 3. Epinephrine and norepinephrine concentrations returned toward control levels in all groups after CPB.

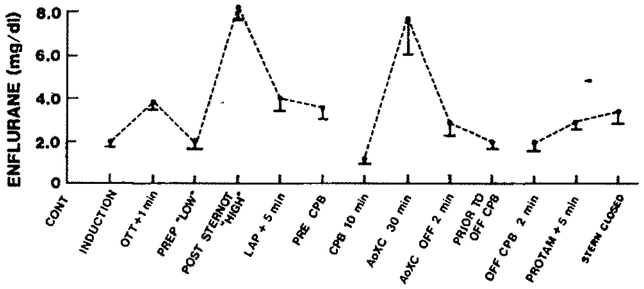

Figure 5. Plot of serum enflurane concentrations (mean ± SEM) vs sample time. See legend to Figure 1 for explanation of abbreviations.

Blood concentrations of drugs during the study are plotted in Figures 4 and 5. The fluctuating serum blood concentrations of the enflurane group (group 3) reflect attempts to stabilize the hemodynamics throughout the operative period. Note the higher peaks at intubation, sternotomy, and midway through CPB when enflurane was used to treat elevated arterial pressures as in the "adjuvant treatment protocol" (Table 1).

Figure 6 plots the infusion of sodium nitroprusside in μg/kg as a function of time before, during, and after CPB and in the CICU. There were no significant differences in the duration of these time periods among groups. There was a significantly greater amount of sodium nitroprusside used during CPB in group 1 patients, and a significantly smaller amount of sodium nitroprusside used in the CICU in group 2 patients. Patients in group 1 received 5.8 ± 1.90 mg of morphine sulfate in the CICU, those in group 2 received 3.2 ± 0.48, and those in group 3 received 10.9 ± 1.49 mg of morphine sulfate.

Table 5 contains data from the period in the intensive care unit. Times to responsiveness and extubation were significantly longer in the supplemented

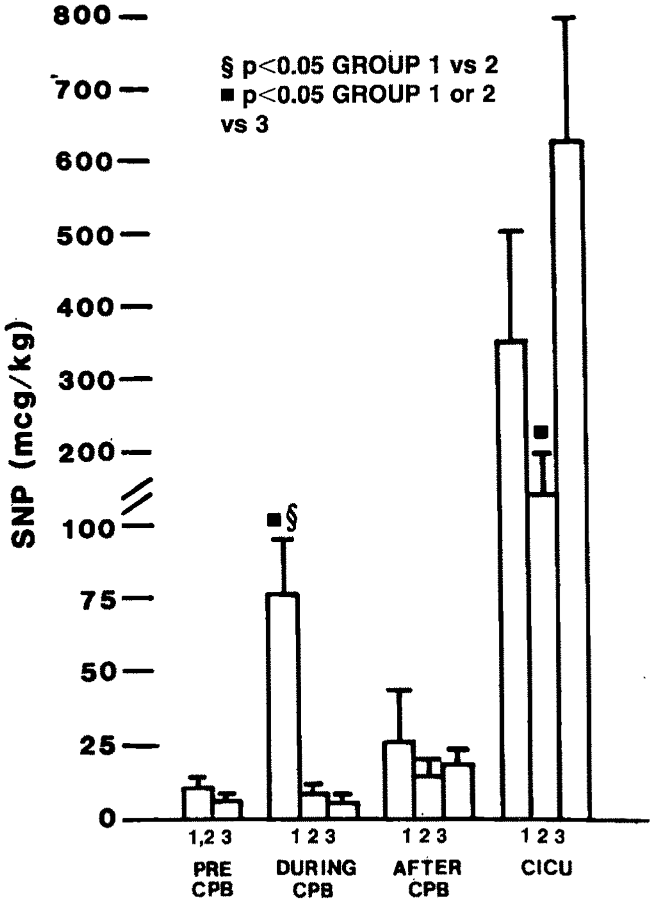

Figure 6. Total infused sodium nitroprusside (μg/kg) (mean ± SEM) vs the perioperative time period (pre, during, and after CPB) and in the intensive care unit. There was no significant difference among groups in the time duration of each of these measurement periods (see Fig. 1).

sufentanil group patients (group 2) than in the enflurane group. Fluid balance (the amounts of crystalloid, colloid, or blood infused; chest drainage; urine output) measured in the CICU was similar in all three groups. There was no difference among the groups in the use of inotropic or antiarrhythmic therapy in the CICU.

Creatine phosphokinase MB fraction (CKMB) levels as a measure of perioperative myocardial necrosis were measured (Table 6). Only three of the 45 patients in the total study population reached CKMB levels greater than 20 IU. At control, prior to CPB, and 8, 10, 12, 24, and 36 hr after initiation of CPB: group 1 patient number 1 had levels of 4, 2, 20, 20, 28, 16, and 8 IU; group 1 patient number 8 had levels of 1, 1, 3, 3, 4, 63, and 22 IU: and group 2 patient number 13 had MB levels of 1, 1, 2, 2, 2, 88, and 4 IU, respectively. Overall CKMB tended to be slightly higher in the unsupplemented sufentanil patients.

Table 5. Intensive Care Unit Data[a]

	Group 1	Group 2	Group 3
Responsive hr after induction	7.5 ± 0.99 (4–13)	8.4 ± 0.66[b] (5–12)	6.4 ± 0.38 (4–12)
Extubation hr after induction	17.9 ± 1.78 (11–24)	19.8 ± 1.00[b] (13–25)	15.8 ± 1.10 (8–23)
Discharge hr after induction	29.9 ± 2.86 (25–47)	28.1 ± 0.84 (24–35)	30.6 ± 2.03 (23–52)
Total crystalloid (ml)	1520 ± 221	1690 ± 90	1680 ± 149
Total colloid (ml)	1000 ± 354	980 ± 168	800 ± 133
Total blood (ml)	680 ± 145	620 ± 132	750 ± 157
Total chest drainage (ml)	990 ± 128[c]	630 ± 57	820 ± 106
Total urine	2190 ± 381	2170 ± 233	1990 ± 250

[a] Data expressed as mean ± SEM with range in parentheses.
[b] $P < 0.05$, group 2 vs group 3.
[c] $P < 0.05$, group 1 vs group 2.
Group 1, unsupplemented sufentanil group; group 2, supplemented sufentanil group; group 3, enflurane group.

Table 6. CKMB Data[a]

	Group 1	Group 2	Group 3
Control	1.6 ± 0.40	1.8 ± 0.63	0.8 ± 0.20
Before CPB	1.5 ± 0.37	1.2 ± 0.45	1.0 ± 0.19
8 hr[b]	5.2 ± 1.96[c,d]	1.8 ± 0.18	2.2 ± 0.30
10 hr	5.6 ± 1.95[c,d]	1.8 ± 0.39	2.4 ± 0.34
12 hr	6.3 ± 2.79[c,d]	1.7 ± 0.30	1.9 ± 0.30
24 hr	11.6 ± 6.62	7.9 ± 6.17	1.9 ± 0.38
36 hr	6.1 ± 2.49	1.5 ± 0.36	1.7 ± 0.32

[a] Creatine phosphokinase MB fraction (CKMB) data expressed as mean ± SEM.
[b] Hr after initiation of CPB.
[c] $P < 0.05$, group 1 vs group 3.
[d] $P < 0.05$, group 1 vs group 2.
Group 1, unsupplemented sufentanil group; group 2, supplemented sufentanil group; group 3, enflurane group.

Discussion

High-dose narcotic anesthesia for patients undergoing cardiac surgery became popularized by the use of morphine in the early 1970s (11). The main attribute appeared to be the maintenance of "hemodynamic stability." Fentanyl, a more potent opioid, replaced morphine as the narcotic of choice during the late 1970s (12). Fewer side effects such as hypotension, prolonged respiratory support, and volume replacement requirements were present with fentanyl (13,14). A search for an even more potent and thus, as the hypothesis goes, a more specific synthetic narcotic continued, resulting in the synthesis of sufentanil. Suppression of the so-called stress response during cardiac anesthesia and surgery was proclaimed as a goal (4).

Sufentanil was found in clinical trials to be five–ten times as potent as fentanyl. Early studies by Sebel et al. and de Lange et al. demonstrated hemodynamic stability in patients with coronary artery disease undergoing myocardial revascularization surgery. These reports suggested that the stress response measured by cortisol and catecholamines was blocked before CPB and perhaps attenuated during CPB (3,15,16).

Previous studies have demonstrated a marked, time-related increase in plasma catecholamine concentrations during nonpulsatile cardiopulmonary bypass (17,18). Thus CPB is an excellent clinical model to study the ability of the newly developed potent opioid to suppress the adrenergic responses to surgical stress. We compared sufentanil–oxygen anesthesia with a nonnarcotic technique control group. By setting blood pressure limits both during and after the operation, we could also quantitate the requirements for vasodilator therapy—in this study, sodium nitroprusside.

Few studies have compared opioid and inhalation anesthetic techniques for cardiac surgery (19). Results of previous studies have generally shown little difference in hemodynamic stability or in variables of outcome (mortality, morbidity, myocardial ischemia) (20–24). What then does our study add to existing knowledge? This is the first study comparing sufentanil anesthesia with an inhalation agent in patients with coronary artery disease. Hemodynamic variables were remarkably stable before and after CPB in both the sufentanil- and enflurane-anesthetized patients. Of note was the considerable fine tuning of the dose of enflurane required to attain this stability (Fig. 5). Also of note is the rapidly declining serum concentration of sufentanil in the single dosed patients (group 1), and the increase in those patients supplemented (group 2) on CPB (Fig. 4). Although no specific serum value for suppression of hypertension during CPB can be assigned, it is clear that the group 2 sufentanil patients had less hypertension and lower catecholamine levels on CPB. Perhaps our 4–5 ng/ml serum level on CPB is approximately equivalent to the 20 ng/ml fentanyl threshold of Wynands et al. (25). The relatively rapid clearance of sufentanil indicates that supplemental sufentanil is required or that constant infusion administration techniques are necessary to block the adrenergic response to CPB. The reader must note that the fentanyl assay utilized by Wynands et al. was the radioimmunoassay (RIA) technique. In contrast, our sufentanil assay was by extraction, gas chromatographic separation, and mass spectrometer detection. The RIA analysis is said to be more sensitive, but was not available to us during this study. Our lower limit of sensitivity of detection was 0.5 ng/ml. Howie et al. have compared RIA and gas chromatographic analysis of sufentanil and reports a 12% coefficient of variation (26). It is of special interest that despite low serum sufentanil concentrations after the operation, there was a decrease in the requirement for sodium nitroprusside in the CICU. This probably reflects the residual analgesic effects of sufentanil, even at quite low plasma drug concentrations. Sufentanil decreases MAC in combination with inhalation agents in animals more so than fentanyl, and thus may be more of an anesthetic than fentanyl (27).

Cardiopulmonary bypass produced an expected two- to three-fold increase in epinephrine and a six- to seven-fold increase in norepinephrine. It is interesting that enflurane at a similar blood concentration, as at sternotomy and on CPB, was able to attenuate the rise in norepinephrine, whereas sufentanil, at a higher blood concentration during CPB (in the supplemented group) than at sternotomy, also suppressed the early rise in norepinephrine (on CPB). The variability among patients for all CPB epinephrine values and later CPB norepinephrine values rendered statistical comparisons insignificant, although clear trends emerged. Whether or not it is desirable to suppress this rise in catecholamines on CPB is unanswered. Although reperfusion of the heart with release of the aortic cross-clamp did not seem to be adversely affected by blood high in catecholamines, there are still a number of potentially undesirable physiologic effects (28).

Postoperative outcome variables examined in this study fail to show a major superiority with any of the anesthetic techniques (29). Serum CKMB levels increased somewhat more in the sufentanil patients (groups 1 and 2), but the levels were extremely low and probably clinically not significant. No postoperative ECGs indicated new myocardial infarction, and no deaths occurred in this study. Clearly analgesia in the CICU was superior in the sufentanil patients, but aside from fewer morphine requirements, this demonstration seems unimportant. The greater use of sodium nitroprusside in the enflurane patients could reflect less analgesia or better cardiac function in the enflurane group. Times of extubation were similar in all groups.

In summary, sufentanil–oxygen anesthesia provided stable hemodynamics before and after CPB—and this was perhaps somewhat more easily attained than in patients anesthetized with enflurane. During CPB, enflurane attenuated the increase in serum norepinephrine concentration, but sufentanil had to be supplemented to attain comparable adrenergic blockade. Patients given sufentanil required less vasodilator than those given enflurane. Maintenance of a higher, more stable blood concentration of sufentanil with infusion techniques might accomplish even better hemodynamic stability during the CPB period (30,31).

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Pharmacokinetics of Fentanyl in Neonates

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KOEHNTOP DE, RODMAN JH, BRUNDAGE DM, HEGLAND MG, BUCKLEY JJ. Pharmacokinetics of fentanyl in neonates. Anesth Analg 1986;65:227–32.

The pharmacokinetics of fentanyl were studied in fourteen neonates undergoing major surgical procedures. Five patients were less than 1 day of age, seven were 1–4 days old, and two were 7–14 days old. Fentanyl was given intravenously, 10 μg/kg (n = 1), 25 μg/kg (n = 4), or 50 μg/kg (n = 9), and plasma concentrations measured at intervals of up to 18 hr. Average weight was 2.9 kg. The injection of 25 or 50 μg/kg of fentanyl over 1–3 min was hemodynamically well-tolerated by all patients. Four newborns without respiratory impairment secondary to surgery or disease needed ventilatory support for an average of 24 hr (range 11–40 hr). Plasma concentrations of fentanyl were most appropriately described by a two-compartment model. The mean ± SEM values of selected model parameters were volume of the central compartment, 1.45 ± 0.34 L/kg; volume of distribution at steady state, 5.1 ± 1 L/kg; clearance, 17.94 ± 4.38 ml·kg^{-1}·min^{-1}; and terminal elimination half-life ($t_{1/2}\beta$), 317 ± 70 min. In seven patients transient rebound in plasma fentanyl concentrations of 0.5 ng/ml or greater occurred. In three patients with markedly increased intraabdominal pressure, the $t_{1/2}\beta$ was 1.5–3 times the population mean. Thus fentanyl disposition in neonates is highly variable, but the $t_{1/2}\beta$ is predictably prolonged in the presence of increased abdominal pressure.

Key Words: ANALGESICS—fentanyl. PHARMACOKINETICS—fentanyl. ANESTHESIA—pediatric.

Although fentanyl is increasingly used to anesthetize critically ill neonates (1), information on its pharmacokinetics in these physiologically unique patients is lacking. Extrapolation of adult fentanyl pharmacokinetic data to neonates is questionable in view of the known age-related differences in body composition, organ development, and drug biotransformation mechanisms. For example, as a percentage of body weight, neonates have a larger total body water content, extracellular fluid compartment, brain, and liver, whereas fat and skeletal muscle tissue is much less compared to that of adults (2).

Changes in organ blood flow during and after surgery may also modify the disposition of fentanyl. For example, in adults the closer the operative site to the liver, the greater the reduction in hepatic blood flow (3). Because the abdomen and liver of a neonate is large relative to the body, the potential for alterations in hepatic blood flow with surgery, particularly abdominal surgery, in these patients may be even greater and further precludes a reliable prediction of fentanyl kinetics in neonates based on adult data. Therefore this study was undertaken to determine the pharmacokinetics of fentanyl after moderate-to-high doses of fentanyl in neonates subjected to surgical procedures. The duration of fentanyl-induced ventilatory depression and its relation to plasma fentanyl concentrations were also examined in selected patients.

Methods

After obtaining ethical committee approval and parental consent, 14 neonates were studied. Table 1 lists each patient's identification number, diagnosis, group designation, age, weight, and fentanyl dose, and divides the patients into three groups according to the site of operation. Group I patients underwent repair of myelomeningocele; groups II and III underwent thoracic and abdominal procedures, respectively. Six neonates were 1 day old or less, and six others were only 2–4 days old. The average weight was 2.9 kg. Surgical relaxation was achieved with pancuronium (0.1 mg/kg), and mechanical ventilation was regulated

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Table 1. Fentanyl Kinetics in Neonates

Patient number	Diagnosis	Age (days)	Weight (kg)	Dose (μg/kg)	Vc (L/kg)	Vdss (L/kg)	TBC ($ml \cdot kg^{-1} \cdot min^{-1}$)	$t_{1/2}\beta$ (min)
Group I								
1	Myelomeningocele	1.0	3.2	50	1.72	2.69	26.80	75
2	Myelomeningocele	0.5	3.3	10	1.37	3.42	20.10	118
3	Myelomeningocele	0.5	3.5	25	0.71	2.66	5.40	441
4	Myelomeningocele	0.5	4.0	50	2.52	9.85	58.70	117
Mean ± SEM		0.6	3.5		1.58	4.66	28.00	188
		± 0.13	± 0.18		± 0.38	± 1.74	± 11.00	± 85
Group II								
5	Sequestered lung	3.0	3.8	50	0.73	2.20	12.80	139
6	Patent ductus arteriosus	7.0	2.5	50	2.68	5.52	20.00	197
7	Patent ductus arteriosus	4.0	2.1	50	0.60	2.30	5.50	315
8	Patent ductus arteriosus	14.0	1.4	50	4.84	13.46	47.40	201
Mean ± SEM		7.0	2.45		2.2	5.87	21.43	213
		± 2.48	± 0.5		± 1.0	± 2.65	± 9.15	± 37
Group III								
9	Diaphragm eventration	2.0	3.3	25	0.10	1.34	9.80	99
10	Duodenal atresia	4.0	3.0	50	0.67	3.8	13.40	223
11	Omphalomesenteric duct	0.5	2.6	25	0.34	1.69	3.40	347
12	Septic ileus	2.0	2.0	25	1.54	4.88	9.10	750
13	Omphalocele	2.0	3.5	50	0.37	7.10	10.70	463
14	Gastroschisis	0.5	1.9	50	2.08	10.49	8.02	956
Mean ± SEM		1.8	2.7		0.85	4.88	9.00	473
		± 0.5	± 0.3		± 0.32	± 1.42	± 1.00	± 132
Combined Mean ± SEM		3	2.9		1.45	5.1	17.94	317
		± 1	± 0.2		± 0.34	± 1.0	± 4.38	± 70

Abbreviations: Vc, volume of the central compartment; Vdss, volume of distribution at steady state; TBC, total body clearance; $t_{1/2}\beta$, terminal elimination half-life.

to maintain $PaCO_2$ between 32 and 40 torr. All patients received an air–O_2 mixture that maintained an arterial of transcutaneous PO_2 between 60 and 80 torr. In addition, 50% N_2O plus 0.2–0.5% halothane of isoflurane was administered to five patients (numbers 1, 2, 3, 4, and 11); 50% N_2O only was used in patients 9 and 10. These inhalation agents were administered to those patients intubated in the operating room and in which positioning and/or placement of a central venous line delayed the injection of fentanyl. Approximately 5 min prior to surgical incision and after 10 ml/kg of fresh frozen plasma had been administered, fentanyl in the doses listed in Table 1 was infused over 1–3 min. In the early stages of the study, the smaller doses and longer infusion periods primarily were used. When it became apparent that circulatory stability was well-maintained even in newborns with rapid infusion of large doses of fentanyl, 50 μg/kg became the preferred dose. Blood samples were collected from an arterial or CVP cannula before and 1, 5, 10, 20, 40, 60, and 120 min after fentanyl had been injected and then intermittently for 3–18 hr thereafter. Plasma was separated and frozen for subsequent analysis by radioimmunoassay. The lower limit of sensitivity was 0.025 ng in an assay volume of 0.5 ml, and the coefficient of variation was 1.6% for a concentration of 1 ng/ml. Each patient's data were fitted to both two- and three linear-compartment models using weighted nonlinear least squares regression. Models were formulated as closed form solutions, and the volume of the central compartment (Vc), intercompartmental rate constants, and elimination rate constant from the central compartment were estimated (4). Terminal elimination half-life ($t_{1/2}\beta$), total body clearance (TBC), and volume of distribution at steady state (Vdss) were calculated. Data were analyzed with both unity weight and the reciprocal of each observation variance squared. Model specification and choice of weights were based on residual analysis, comparative absolute (unweighted) sum of squares, and correlation of observed and predicted observations. Results are expressed as means ± SEM. For statistical comparison, ANOVA and *t*-test were used where appropriate. The Wilcoxon rank sum test

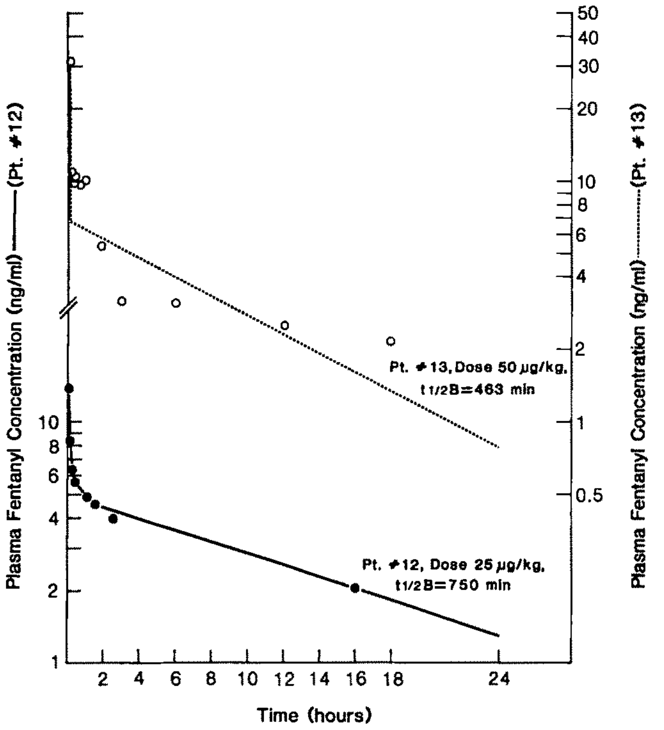

Figure 1. Plasma fentanyl concentrations in two neonates (2 days old) with increased intraabdominal pressure and prolonged $t_{1/2}\beta$. Model predictions for patient 13, dashed line; patient 12, solid line. Measured concentrations for patient 13, unfilled circles; patient 12, filled circles. Note that the concentration ordinate for patient 13 is different from patient 12.

Abbreviation: Pt. #, patient number.

was used to compare pharmacokinetic parameters among groups. A P value of less than 0.05 was considered significant.

Results

The injection of 25 or 50 μg/kg of fentanyl over 1–3 min was hemodynamically well-tolerated by all patients. The average time from injection of fentanyl to end of surgery was 109 ± 13 min (range 50–170 min). Plasma concentration data of fentanyl were most appropriately described by a two-compartment model. Table 1 lists selected pharmacokinetic model parameters for each patient. No significant difference in the pharmacokinetic parameters was found for dose, or among premature infants, full-term infants up to the age of 24 hr, and older neonates. The large variability in pharmacokinetic parameters among patients was particularly noteworthy in group I because it had the most homogeneous population with respect to surgical procedure, age, and size.

In spite of a noticeably progressive increase in the $t_{1/2}\beta$ and a decrease in the TBC from surgical group I to II, and from group II to III, no statistical difference in any of the parameters was found between these three groups. However, if the three patients (numbers 12, 13, and 14) with markedly increased intraabdominal pressure due to closure of a large abdominal defect or distended bowel are compared to the others, the increases in their fentanyl $t_{1/2}\beta$ (1.5–3 times the population mean of 317 min) was statistically significant. Figure 1 illustrates the plasma fentanyl curves for two of these group III neonates with markedly increased intraabdominal pressure. Patient number 12 underwent an exploratory laparotomy for suspected bowel obstruction and was found to have a septic ileus. He received 25 μg/kg of fentanyl, and the $t_{1/2}\beta$ was 750 min compared to population mean of 317 min. Patient 13 had a repair of a large omphalocele. He received 50 μg/kg of fentanyl, and the $t_{1/2}\beta$ was 463 min. The plasma concentration of fentanyl at 1 min in patient 12 was approximately half the 1-min value of 32 ng/ml for patient 13 and by 18 hr had decreased to only 2 ng/ml in both patients. Interestingly we observed that the three neonates (numbers 12, 13, and 14) with increased abdominal pressure did not exhibit a rebound in plasma fentanyl levels of 0.5 ng/ml or greater, whereas the other three neonates in group III did manifest this rebound.

Table 2. Time Course and Extent of Fentanyl Rebound in Neonates

Patient Number	Time of onset (minutes after injection)	Extent of rebound (ng/ml)
2	10	0.5
3	10, 60, 900	5.0, 7.0, 1.5
5	40	6.3
8	120	0.8
9	40	2.0
10	360	1.8
11	10, 60, 360	6.0, 5.0, 2.5
Mean ± SEM		3.5 ± 0.7

Table 2 lists the seven patients from all three groups who displayed a transient rebound in plasma fentanyl levels of 0.5 ng/ml or greater along with the time of onset and extent of rebound. No pattern with regard to time of onset is evident. Patients 3 and 11 each had three subsequent transient increases in plasma fentanyl levels. The average increase for all seven patients was 3.5 ng/ml. Patients 3 and 11 not only had the three transient increases in plasma fentanyl concentrations but also required markedly prolonged ventilatory support.

Table 3. Characteristics of Prolonged Fentanyl-Induced Ventilatory Depression in Neonates with No Respiratory Impairment Secondary to Surgery or Disease

Patient number	Age (days)	Weight (kg)	Dose (μg/kg)	Plasma fentanyl concentration (ng/ml) (hr after injection)[a]	Duration of intubation (hr)	Calculated plasma fentanyl concentration at time of extubation (ng/ml)[b]
1	1.0	3.2	50	3.8 (3 hr)	11	0.05
3	0.5	3.5	25	3.5 (15 hr)	27	0.50
4	0.5	4.0	50	1.1 (16 hr)	17	0.77
11	0.5	2.6	25	3.0 (16 hr)	40	0.17

[a] Last measured plasma fentanyl concentration ($Cp_{(L)}$).

[b] Calculated plasma fentanyl concentration $= Cp_{(L)}\, e^{-\frac{0.693T}{t_{1/2}\beta}}$; T = time from $Cp_{(L)}$ to extubation.

Table 3 details the age, weight, fentanyl dose, last measured plasma fentanyl concentration, and duration of intubation in the four neonates who required prolonged ventilatory assistance after 25 or 50 μg/kg of fentanyl despite the fact that their disease imposed no respiratory dysfunction. After the last fentanyl sample, naloxone transiently reversed the respiratory depression. The decision to extubate was made by the pediatric intensive care staff and was based primarily on the attainment of a Pa_{CO_2} of less than 41 torr and satisfactory oxygen tensions with inspired oxygen fractions ranging between 0.21 and 0.40 during spontaneous ventilation. Note that all four of these neonates were 24 hr old or less and weighed between 2.6 and 4 kg.

Discussion

Moderate to high-dose fentanyl in our fourteen neonates resulted in mean values of $t_{1/2}\beta$, TBC, Vc, and Vdss larger than those reported in adults (5). Similar age-related pharmacokinetic differences between two neonates and four adults were recently reported by Johnson et al. (6). The adults had a mean Vc of 0.14 L/kg and Vdss of 1.61 L/kg, which was significantly different from the Vc of 1.73 L/kg and Vdss of 5.94 L/kg for the two neonates they studied. Neonatal values in their patients are in close agreement with the Vc of 1.45 L/kg and Vdss of 5.1 L/kg in our fourteen neonates. The $t_{1/2}\beta$ and TBC were also quite similar, i.e., 317 min and 17.94 ml·kg^{-1}·min^{-1} in our study compared to 294 min and 16.2 ml·kg^{-1}·min^{-1} in their study. In contrast, the adults in the study by Johnson et al. had a $t_{1/2}\beta$ of 129 min and TBC of 10 ml·kg^{-1}·min^{-1}.

The implications of the larger Vc and Vdss in neonates compared to adults are, first, that the initial and steady state neonatal plasma fentanyl concentrations will be lower for the same μg/kg dose and, second, that fentanyl elimination will be prolonged. However, the highly variable pharmacokinetic parameters in our neonates preclude predicting this behavior with certainty in individual neonates. The variability appears to be related in part to the site and type of surgical lesion. For example, neonates with increased abdominal pressure had substantially greater $t_{1/2}\beta$ than the other patients. This suggests retention of fentanyl in a poorly perfused compartment, diminished splanchnic and hepatic blood flow, or both, which could be expected to delay biotransformation and elimination. Fentanyl has a high hepatic extraction ratio, and thus clearance is primarily dependent on hepatic perfusion (7). Consequently, the decrease in hepatic blood flow that occurs with increased abdominal pressure will slow fentanyl clearance. Masey et al. found a 40% decrease in liver blood flow and a 21% decrease in cardiac output when the intraabdominal pressure in newborn lambs was 20 mm Hg (8). Intragastric pressures of 20 mm Hg have been recorded during repair of omphalocele and gastroschesis (9). The decrease in cardiac output secondary to increased intraabdominal pressure also contributes to reduction in the clearance of fentanyl because low cardiac output retards the transfer of fentanyl from peripheral tissues to the plasma. This transfer has been identified as the rate-limiting step in the removal of fentanyl from the body (10).

The transient rebounds in fentanyl plasma levels that occurred in seven patients may reflect sequestering and subsequent release of fentanyl, and were not well-described by a compartmental model. Similar rebounds in fentanyl plasma levels have been reported by others in adults (10–14). Stoeckel et al. demonstrated biphasic depression of the carbon dioxide response curve secondary to increases in the plasma fentanyl concentration 45–60 min after injection (11). Others have reported secondary fentanyl peaks during the first 5 min after injection (12), within 45 min of the end of surgery (13), 20–90 min after injection (14), and at 2–4 hr and again at 5–7 hr after injection (10). Similarly, in our neonates the fentanyl rebound occurred anywhere from 10 min to 15 hr after injection. The two patients (numbers 3 and 11) who had three transient increases in plasma fentanyl levels were also the same patients who required markedly prolonged ventilatory support and intubation (Table 3). These two full-term newborns had no surgical or other disease which could explain this respiratory depression. It is compatible with prolonged $t_{1/2}\beta$ and low TBC but may also reflect an increased sensitivity to the respiratory depressant effects of fentanyl. Because a strong correlation exists between the concentration of fentanyl in plasma and in cerebrospinal fluid and the degree of respiratory depression (15), evidence suggestive of increased sensitivity in neonates would be a lower plasma fentanyl concentration at which respiratory recovery permits extubation. The mean fentanyl concentration at the time of extubation in these four neonates was calculated to be 0.37 ng/ml (range 0.05–0.77 ng/ml) (Table 3). In adults higher plasma fentanyl levels are generally required before ventilatory depression is seen. Cartwright et al. found that 50% depression of the CO_2 response curve in adult patients occurred when plasma fentanyl concentration reached 2.0–3.1 ng/ml (16). They chose 50% depression of the CO_2 ventilatory response curve as a sensitive index of ventilatory depression because, at this point on the curve, resting ventilation was sufficiently depressed to cause elevation of the Pa_{CO_2} above 45 torr. In another study, fentanyl plasma levels of 4.6 ng/ml were necessary to produce 50% depression of the CO_2 response curve in healthy adult volunteers (17). Lehmann et al. observed no clinically relevant respiratory depression in adults when plasma fentanyl concentration was 0.2–6.8 ng/ml (18). Thus when our newborn results are compared to these findings in adults, a logical conjecture is that the newborns we studied were more sensitive to the respiratory depressant effect of fentanyl. Factors contributing to this increased sensitivity were not determined, but in the case of morphine it is most likely due to the greater permeability of the newborn brain to morphine (19,20). Whether any further increase in permeability to the highly lipid-soluble narcotic, fentanyl, can occur is unknown. The extent to which lower brain myelin content, higher cerebral blood flow, altered protein binding (2), and differences in respiratory control mechanisms in immature newborns (21–23) affect the sensitivity to fentanyl also has not been investigated.

In conclusion, both pharmacodynamic and pharmacokinetic mechanisms appear to be responsible for the extremely prolonged ventilatory depression that can occur in newborns after fentanyl anesthesia. The highly variable disposition of fentanyl in neonates further compounds the difficulty of predicting full and permanent ventilatory recovery after fentanyl anesthesia. In those neonates with increased intraabdominal pressure, the $t_{1/2}\beta$ will be predictably prolonged.

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Comparative Pharmacokinetics and Dynamics of Vecuronium and Pancuronium in Anesthetized Patients

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SOHN YJ, BENCINI AF, SCAF AHJ, KERSTEN UW, AGOSTON S. Comparative pharmacokinetics and dynamics of vecuronium and pancuronium in anesthetized patients. Anesth Analg 1986;65:233–9.

Plasma concentrations and the degree of neuromuscular blockade after a 2-min infusion of 0.1 mg/kg of vecuronium bromide or pancuronium bromide (equipotent doses) were studied in 12 gynecologic patients. The plasma concentrations of both drugs declined in a triphasic manner. The difference between the intercepts and rate constants of the two drugs was not significant. Vecuronium was removed faster from the plasma than pancuronium; this was reflected in a significantly larger plasma clearance rate for vecuronium (4 ml·min^{-1}·kg^{-1} vs 1.1 ml·min^{-1}·kg^{-1} for pancuronium). The effective plasma concentrations at 50% recovery of the twitch height were 0.11 ± 0.02 (vecuronium) and 0.2 ± 0.03 μg/ml (pancuronium). The disposition kinetics were adequately described by a three-compartment model. An effect compartment was added to the model to correlate the neuromuscular effects and plasma concentrations of both drugs. The ratio between concentrations of vecuronium and pancuronium in the effect compartment at 50% twitch height was 0.83. In spite of its greater potency, vecuronium has a shorter duration of action than pancuronium.

Key Words: NEUROMUSCULAR RELAXANTS—pancuronium, vecuronium. PHARMACOKINETICS—pancuronium, vecuronium.

The recently introduced muscle relaxant, vecuronium bromide, has a shorter duration of action and a more rapid recovery than its bisquaternary homologue pancuronium (1–4). Early studies of the pharmacokinetics of vecuronium in dogs (5) and humans (6,7) suggested that the shorter duration of action of vecuronium could be attributed to its shorter terminal half-life and relatively larger plasma clearance when compared to pancuronium. This conflicted with our findings in an earlier pilot study (8) where the decline of vecuronium plasma concentration was resolved into three exponential terms with a terminal half-life that did not seem to differ significantly from that of pancuronium as reported in other studies (9–11).

This prompted us to study the pharmacokinetics and dynamics of vecuronium and pancuronium in similar clinical conditions after the administration of equipotent doses of vecuronium and pancuronium using a more sensitive assay method, namely fluorimetric analysis (lower limit of detection, 5 ng/ml).

Methods

This study was approved by the Ethics Committee of the University Hospital of Groningen. All 12 patients gave their informed consent to participate in the study at the preoperative visit.

The patients were between 20–70 years of age and all had a preoperative ASA status of either I or II. All patients underwent minor gynecologic procedures that did not cause loss of more than 20% of the blood volume. No patient was being treated with medications known to interfere with the effect of neuromuscular blocking agents.

Anesthesia

Patients were premedicated with pantopon (Omnopon), 0.2 mg/kg, and atropine, 7 μg/kg intramuscularly, 45 min before the start of the operation. Anesthesia was induced with thiopental, 3–5 mg/kg, followed by fentanyl, 1.5 μg/kg. Tracheal intubation was facilitated by succinylcholine, 1 mg/kg. Artificial ventilation was commenced, and anesthesia was

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maintained with 33% oxygen in nitrous oxide and 0.5% halothane. Fentanyl in fractional doses of 1.5 μg/kg was added as required (total dose 0.5 ± 0.2 mg). The esophageal temperature stayed between 35.5–37°C during the studies, and the end-tidal CO_2 remained between 4 and 5 kPa.

Experimental Procedure

The neuromuscular effects of both pancuronium and vecuronium were monitored by measuring the twitch tension of the adductor pollicis muscle. This was indirectly stimulated, every 10 sec, by single supramaximal square-wave electrical impulses of 0.2 msec, applied to the ulnar nerve at the wrist. The force of the resultant contraction of the adductor pollicis muscle was sensed by a force displacement transducer (Statham UC3) taped in the patients' fists and recorded on a Gould Brush recorder generated by a Myotest nerve stimulator. Neuromuscular monitoring was commenced immediately after induction of anesthesia and the twitch height recording allowed to stabilize for 10 min before tracheal intubation. After the administration of succinylcholine for intubation, the twitch height was allowed to recover to 100% of the control value and to stabilize for a further 10 min. Vecuronium (n = 7) or pancuronium (n = 5), 0.1 mg/kg, dissolved in 10 ml sterile water, was then injected over 2 min in a rapidly running infusion in the arm opposite to that used for blood sampling.

Samples of blood, each of 8 ml, were collected from a peripheral vein in the arm opposite to that used for infusion of drugs. Blood was sampled several minutes before and 1, 3, 5, 7, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, and 300 min after the administration of the neuromuscular blocking agent. Additional blood samples were obtained at 50% recovery of the twitch. All samples were immediately buffered with 2 ml of a 1M disodium hydrogen phosphate solution to a pH of 4 to prevent degradation of the vecuronium in vitro (Appendix 1). Samples were then centrifuged and the separated plasma deep-frozen to await further analysis.

Chemical Analysis

Concentrations of vecuronium or pancuronium in the plasma were measured by a modified fluorimetric assay that was originally described for pancuronium by Kersten et al. (12). This modified technique has a detection limit of 5 ng/ml of plasma and the coefficient of variation is 3–10% in the 5–1000 ng/ml range. Each sample was then further analyzed by thin-layer plate chromatography to distinguish vecuronium or pancuronium and their putative metabolites from one another. The density and size of the spots on the plate were compared to those produced by known amounts of the reference compounds. The error of this semiquantitative technique is about 10%, and as little as 150 ng of a compound can be detected.

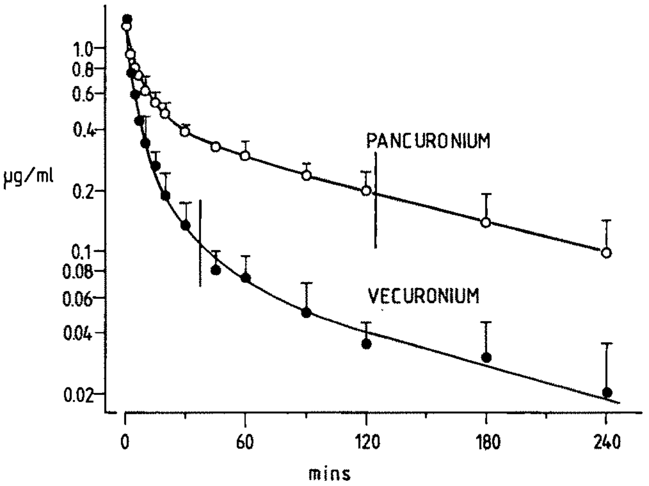

Figure 1. Plasma concentrations of vecuronium and pancuronium after 0.1 mg/kg, intravenously. ○, mean. T, SEM. Vertical bars bisecting plasma curves indicate plasma concentration at 50% recovery (for vecuronium, 0.11 ± 0.02 μg/ml (mean ± SD); for pancuronium, 0.2 ± 0.03 μg/ml).

Pharmacokinetic Analysis

Individual plasma curves were analyzed by a computer program written by one of us (AHJS). This reiteratively peels the experimental data plotted on a semi-log scale using linear regression analysis. Plasma curves could be resolved into up to five residual exponential terms. The number of terms best fitting the experimental data was then determined by using the statistical criteria described by Boxenbaum et al. (13). The calculated intercepts of the residual exponential functions were corrected to allow for the 2-min infusion of the muscle relaxant (14). Microparameters of the models describing the plasma curves were calculated using standard equations (15). An effect compartment was added to the model to correlate the plasma concentrations with the neuromuscular blocking activity of the investigated compound. This is described in detail in Appendix 2.

Statistical Analysis

For the statistical analysis of the data the Wilcoxon rank sum test was used. The null hypothesis was rejected at the 5% level of significance.

Table 1. Macroparameters of the Plasma Concentration–Time Curves of Vecuronium and Pancuronium

	Vecuronium	Pancuronium
C_1 (μg·ml^{-1})	1.07 (84%)	0.80 (25%)
C_2 (μg·ml^{-1})	0.45 (63%)	0.36 (58%)
C_3 (μg·ml^{-1})	0.06 (54%)	0.18 (164%)
λ_1 (min^{-1})	0.54 ± 0.3	0.25 ± 0.13
λ_2 (min^{-1})	0.069 ± 0.029	0.031 ± 0.031
λ_3 (min^{-1})	0.0059 ± 0.0036	0.0036 ± 0.0023
(t½)$_1$ (min)	1.27	2.57
(t½)$_2$ (min)	10.00	22.60
(t½)$_3$ (min)	116.00	190.00
$V_D$ss (L·kg^{-1})	0.48 ± 0.27	0.29 ± 0.15
Cl (ml·min^{-1}· kg^{-1})	4.00 ± 1.78[a]	1.10 ± 1.64[a]

C_1–C_3 are the intercepts on the ordinate (plasma concentration) of the plasma concentration–decay curve at time = zero of the component exponential functions forming the polyexponential plasma decay curve; the subscripts 1–3 refer to the component exponential curves. λ_1–λ_3 are the rate constants describing the speed of decrease of the component exponential curves forming the plasma concentration–decay curves. (t½)$_1$–(t½)$_3$ are the half-lives of the component exponential curves forming the plasma concentration decay curve. $V_D$ss is the apparent volume of distribution at steady state conditions. Cl is the total body clearance.

Because the plasma concentration curves were plotted on a semi-log scale, the intercepts C_1–C_3 are presented as mean and % coefficient of variation in brackets.

All other data is presented as mean ± SD.

[a] Significant difference between vecuronium and pancuronium.

$P < 0.05$; Wilcoxon rank sum test.

Results

Plasma Concentrations

The decreases of the plasma concentrations of vecuronium and pancuronium are compared in Figure 1. In most of the patients the plasma concentration decay curve could best be resolved into three exponential terms, macroparameters of which are listed in Table 1.

Due to the rather large variation, none of these macroparameters differed significantly between vecuronium and pancuronium. However, the areas under the curve and thus the clearance values of pancuronium and vecuronium differed significantly (Table 1). Vecuronium was accordingly removed more rapidly from the plasma such that the effective plasma concentration corresponding with 50% recovery of the twitch height was reached within 45 min after the injection of vecuronium in contrast to about 120 min after pancuronium (Fig. 1).

The disposition kinetics of both muscle relaxants could best be represented by a three-compartment model (Fig 2, inset). The microparameters of the models for vecuronium and pancuronium are compared in Table 2.

The distribution rate constants (k_{13}) as well as the elimination rate constant (k_{10}) of vecuronium were three and five times higher than those of pancuronium, respectively.

Effect–Concentration Relationships

Using the above-mentioned model, we plotted the time course of the concentration of vecuronium and pancuronium in the three compartments of the model (Fig. 2). The relationship between the concentration of vecuronium in each compartment and its neuromuscular blocking effects was then plotted as shown in Fig. 3.

The large degree of hysteresis shown by the curves for all three compartments of the model indicates poor correlation between the mean concentration of vecuronium in these compartments and effect. Figure 4 correlates the neuromuscular blocking effects and concentrations of both drugs in the effect compartment, which had to be added in order to allow good correlation of the tissue concentration and effect. Figure 5 shows the course of the neuromuscular blockade simulated by this model superimposed on the averaged experimental data. The fit of the simulated curves to the measured points is very adequate.

Discussion

It is apparent from this study that the basis of the shorter action and recovery of vecuronium when compared to pancuronium is the more rapid removal of vecuronium from the plasma so that the plasma concentration corresponding to 50% recovery of the twitch height is reached earlier with vecuronium. The reasons for this more rapid efflux of vecuronium from the plasma are not discernible from the residual plasma curves because there is no significant difference between the parameters of the two drugs. The model microparameters, however, identify two processes that could contribute to the rapid removal of vecuronium from the plasma, namely, a faster rate of transfer of vecuronium from the central compartment to the deep peripheral tissues (k_{13}) as well as a larger rate of elimination of vecuronium (k_{10}) (see Table 2). The brisker elimination of vecuronium (as indicated by the larger rate constant of the terminal phase of the decay curve of vecuronium) is supported by the majority of the available studies on the pharmacokinetics of vecuronium and pancuronium (7,9–11,18). The contribution of the distributive element to the rapid plunge of the vecuronium plasma concentration is, however, ignored by most of these studies. It has been sug-

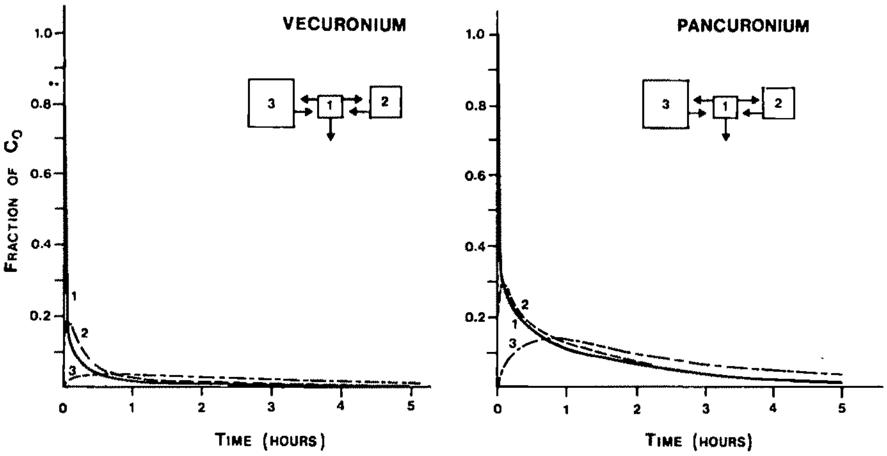

Figure 2. Concentrations of vecuronium or pancuronium in the three compartments of the pharmacokinetic model (*inset*).

Table 2. Kinetic Microparameters of Disposition Models for Vecuronium and Pancuronium

	Vecuronium	Pancuronium
V_1 (L·kg^{-1})	0.048 ± 0.02	0.061 ± 0.014
V_2 (L·kg^{-1})	0.054 ± 0.031	0.073 ± 0.041
V_3 (L·kg^{-1})	0.38 ± 0.22	0.16 ± 0.12
k_{12} (min^{-1})	0.23 ± 0.18	0.12 ± 0.09
k_{21} (min^{-1})	0.19 ± 0.12	0.11 ± 0.062
k_{13} (min^{-1})	0.086 ± 0.024[a]	0.026 ± 0.024[a]
k_{31} (min^{-1})	0.013 ± 0.007	0.014 ± 0.016
k_{10} (min^{-1})	0.099 ± 0.049[a]	0.019 ± 0.0046[a]

V_1–V_3 are the volumes of distribution of the three compartments (hence subscripts 1–3) forming the kinetic disposition model.

k is the rate of transfer of drug from one compartment to the other; the direction of transfer is denoted by the subscripts 0–3 where 0 means extracorporeal, and 1–3 refer to compartments 1, 2, 3, respectively, of the disposition model. Thus k_{12} refers to the rate of transfer of drug from compartment 1 to compartment 2 and so on.

All data presented as mean ± SD.

[a] Significant difference between vecuronium and pancuronium. $P < 0.05$; Wilcoxon rank sum test.

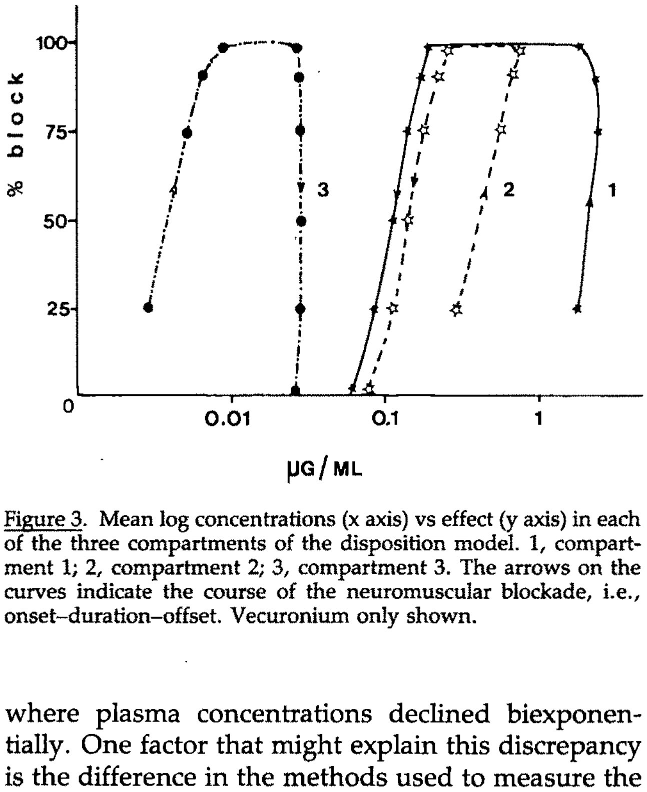

Figure 3. Mean log concentrations (x axis) vs effect (y axis) in each of the three compartments of the disposition model. 1, compartment 1; 2, compartment 2; 3, compartment 3. The arrows on the curves indicate the course of the neuromuscular blockade, i.e., onset–duration–offset. Vecuronium only shown.

gested that, in humans (20), this rapid distribution is related to rapid uptake of vecuronium into the liver.

The effective plasma concentration at 50% recovery of the twitch height of vecuronium is almost half that of pancuronium (0.11 vs 0.20 µg/ml, respectively). However, in view of the more rapid distribution of vecuronium to the deep peripheral tissues, no conclusion can be drawn as to the potency of vecuronium, relative to pancuronium, from these data alone. The effective concentration of the drugs in the postulated effect compartment at 50% twitch height could, however, allow a more adequate comparison. Evaluated in this way the potency ratio of vecuronium to pancuronium is about 0.83 (0.15:0.18 µg/ml).

In this study, the decay of the plasma concentration of vecuronium occurred in a triexponential manner, in contrast to that described in earlier studies (6,7) where plasma concentrations declined biexponentially. One factor that might explain this discrepancy is the difference in the methods used to measure the plasma concentrations. In one study (6), plasma concentrations of vecuronium, measured by the relatively insensitive high-performance liquid chromatography—lower limit of detection 50 ng/ml (16)—could be observed for only 90 min after the injection of vecuronium. Consequently, the larger part of the slower, terminal elimination phase was probably not detected. In the other study, which also made use of high-performance liquid chromatography (7), large doses (>4.5 times the ED_{90}) had to be employed in order to observe the plasma concentrations for a longer period. Large doses could, however, lead to nonlinear processes (17) with consequent flattening of the dis-

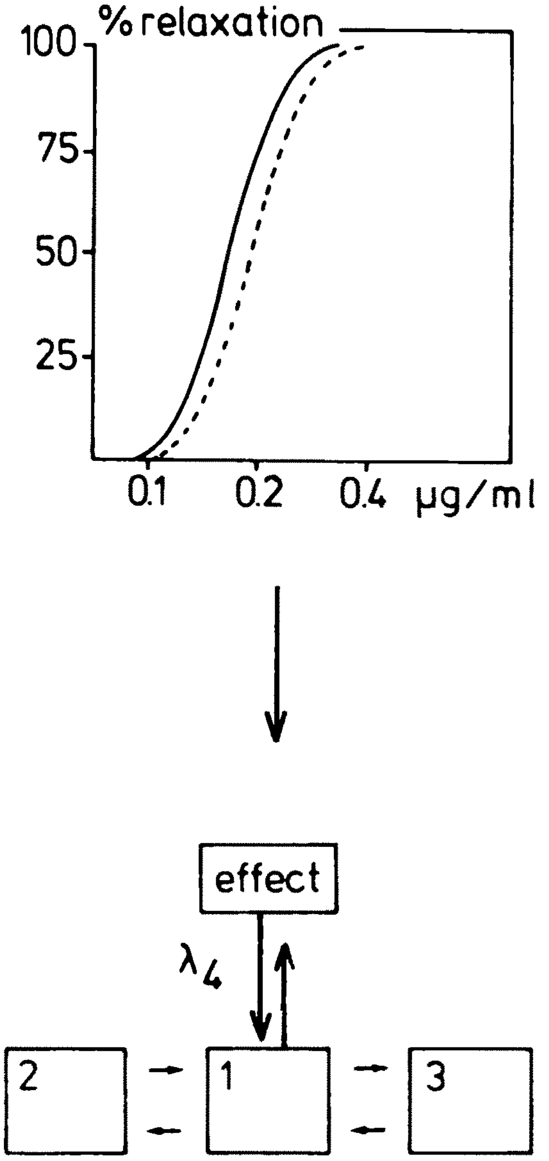

Figure 4. Curves of log concentrations in effect compartment (x axis) vs relaxant effect (adductor pollicis) (y axis) for vecuronium (——) and pancuronium (---). λ_4, Transfer rate constant (for vecuronium, 0.114 min^{-1}; for pancuronium, 0.146 min^{-1}) between effect compartment and driving compartment (compartment 1). The ratio of the concentration of vecuronium to pancuronium in the effect compartment at 50% twitch height = 0.83 (0.15/0.18 µg/ml).

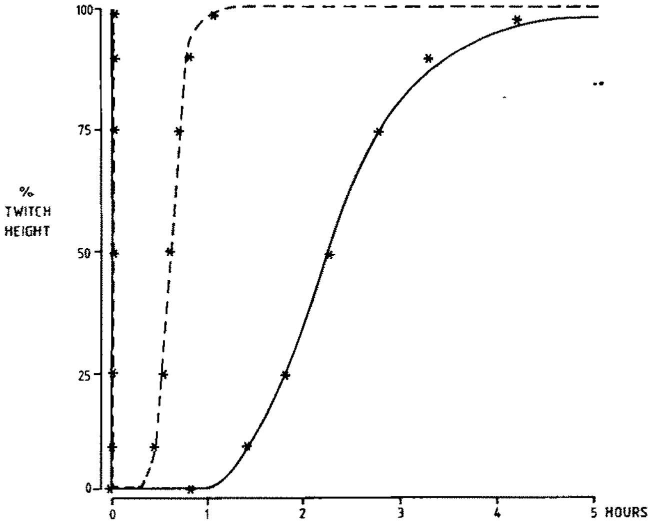

Figure 5. Simulated course of neuromuscular blocking effects using effect compartment (curves) superimposed on experimental data points (*). Pancuronium (———), vecuronium (----).

tribution slopes of the plasma concentration decline and merging of the early and late distribution slopes into one. In a more recent study that used the very sensitive mass spectral analysis to measure the plasma concentration (level of detection 2 ng/ml), Cronnelly et al. found that the plasma concentration–decay curve of vecuronium was also resolved into three residual exponential terms (18).

Contrary to our finding in the present study, Cronnelly et al. (18) calculated a terminal half-life for vecuronium that was significantly shorter than that of pancuronium. This disparity between the present study and that of Cronnelly et al. could possibly be attributed to methodologic shortcomings in both these studies. Cronnelly et al. do not mention whether they buffered the plasma samples to prevent in vitro degradation of vecuronium, which is known to occur to a substantial degree above a plasma pH of 4 (Appendix 1). Because these workers measured exclusively unchanged vecuronium by means of mass spectrometry (a method that besides being very sensitive is also very selective in that it can measure the parent compounds and their metabolites separately) (19), this could well have resulted in considerable underestimation of the original concentration of vecuronium in the blood samples before in vitro degradation occurred. This could, consequently, account for the significant difference in the terminal half-lives of vecuronium and pancuronium found in that study (18).

In contrast, the combined fluorimetric–chromatographic assay used in our study is probably not specific enough to differentiate vecuronium from each of its metabolites at lower plasma concentrations. The determination of the aggregate concentration of vecuronium and its metabolites during the terminal phase of the decline of vecuronium plasma concentration possibly led to an overestimate of the half-life of this phase. This could explain why we failed to observe any significant difference between the terminal half-lives of vecuronium and pancuronium in the present study. A separate study of the pharmacokinetics of the metabolites by mass spectrometry should provide a conclusive answer to these questions.

In conclusion, this investigation has shown that, when compared to pancuronium, vecuronium is removed from the plasma more rapidly so that ineffective plasma concentrations are attained sooner than with pancuronium. It seems that this more rapid plasma efflux of vecuronium is due both to a faster rate of elimination as well as to a more rapid transfer of vecuronium to peripheral tissues. Based on the effective concentration in the effect compartment, vecuronium is apparently only slightly more potent than pancuronium.

Appendix 1

The information below was generated and provided by Drs. J. Paanakker and G. v.d. Laar of the Scientific Development Group of Organon International BV, Oss, The Netherlands.

Table A1. Rate of In Vitro Degradation of Vecuronium in Plasma under Different pH and Temperature Conditions

Temperature (°C)	pH	Storage (hr)	% Vecuronium unaltered
22	7.4	1.5	72
22	7.4	4	51
22	7.4	24	7
22	4	1.5	100
22	4	4	100
22	4	24	100
4	7.4	1.5	100
4	7.4	4	85
4	7.4	24	35

Appendix 2

Addition of an Effect Compartment to the Three-Compartment Disposition Model of Vecuronium and Pancuronium. The following symbols are used in the mathematical analysis that follows:

n, number of compartments of the disposition model.

b, the effect compartment $= n + 1$.

i, 1, . . . n and stipulates a compartment of the disposition model.

j, 1, . . . n and stipulates a phase or exponential of the amount vs time curve in each compartment of the disposition model.

A, amount of drug in a compartment.

$A(t)_b$, amount of drug in effect compartment at time t.

X_{ij}, intercept of exponential j in compartment i of the amount vs time curve.

k, transfer rate constant.

λ, hybrid rate constant.

V, volume of a compartment.

AUC, area under the curve.

Using the principle described by Hull et al. for pancuronium (21), we considered the biophase compartment to be of such small dimensions that the flow of drug to and from this compartment would not have any discernible effect on the amount of drug that is distributed throughout the three compartments of the disposition model. With this proviso, the change of the amount of drug in the effect compartment is described by Equation 1:

$$\frac{dA(t)_b}{dt} = k_{ib} \sum_{j=1}^{n} X_{ij} e^{-\lambda_j t} - k_{bi} A(t)_b \qquad (1)$$

Note that in equation (1), X_{ij} is the intercept of compartment i in phase j and has, therefore, here the dimensions of amount and not of concentration.

Solving Equation 1 by integration gives the following equation:

$$A(t)_b = k_{ib} \left\{ \sum_{j=1}^{n} \frac{X_{ij}}{k_{bi} - \lambda_j} e^{-\lambda_j t} + \left(\sum_{j=1}^{n} \frac{X_{ij}}{\lambda_j - k_{bi}} \right) e^{-\lambda_b t} \right\} \qquad (2)$$

It is evident from Equation 2 that the time course of the amount of vecuronium or pancuronium in the effect compartment $A(t)_b$ is not affected by the rate constant k_{ib} determining the transfer of the drugs from one of the compartments of the disposition model to the effect compartment. This constant can, therefore, be disregarded; and only k_{bi}, the rate constant determining the efflux of the drugs from the effect compartment to one of the disposition model compartments, needs to be calculated.

To compute k_{bi} Equation 2 was reiteratively solved for varying values of k_{bi} from 0 to 1 and for values of $i = 1, \ldots n$. The logarithm of the amount of drug in the effect compartment calculated in this way was then plotted each time against the logit transformation of the effect (twitch height) (Hill transformation) until the scatter was least. This was found to be so when: 1) the value of k_{bi} was 0.114 min^{-1} and 0.146 min^{-1} for vecuronium and pancuronium, respectively; and 2) while the effect compartment was driven by compartment one of the disposition model.

In order to calculate the change of concentration in the effect compartment, the amount in this compartment, computed as described above, was related to the volume of distribution of this compartment which was in turn calculated from Equation 3:

$$V_b = V_i \times AUC_b/AUC_i \qquad (3)$$

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The Effect of Acute Hypocapnia on Human Median Nerve Somatosensory Evoked Responses

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SCHUBERT A, DRUMMOND JC. The effect of acute hypocapnia on human median nerve somatosensory evoked responses. Anesth Analg 1986;65:240–4.

This study was undertaken to define the effect of acute hypocapnia on intraoperatively recorded somatosensory evoked potentials (SSEPs). Median nerve SSEPs were studied in ten anesthetized neurologically normal adult patients undergoing elective nonneurologic surgery. End-tidal carbon dioxide tension ($ETco_2$) was allowed to stabilize for 15 min before SSEP recordings were obtained during normocapnia (N) ($ETco_2$ = 39.9 ± 1.45 mm Hg), hypocapnia (H) ($ETco_2$ = 20.6 ± 1.07 mm Hg), and after return to normocapnia (NR). Although a trend toward a reduction in the latencies of all SSEP components was evident, only the cervical (C_{II}), and cortical (N_1 and P_1) latencies decreased significantly with H when compared to N. Mean latencies for C_{II}, N_1, and P_1 (± SD) were, respectively, 14.80 ± 1.14, 20.93 ± 1.50, and 25.17 ± 2.88 msec during N, and 14.50 ± 1.13, 20.25 ± 1.49, and 24.23 ± 2.52 msec during H. On return to normocapnia, latencies were unchanged from N. Cortical latencies were affected to a greater extent than subcortical ones. Aside from a small but statistically significant increase in C_{II} amplitude at H (2.05 ± 0.55 μV vs 1.83 ± 0.49 μV at N), SSEP amplitudes were unaffected by hypocapnia. The authors conclude that acute hypocapnia in neurologically normal patients results in a small reduction of SSEP latencies. The magnitude of the change is such that it is unlikely to interfere with recording or interpretation of intraoperative SSEPs.

Key Words: BRAIN, EVOKED POTENTIALS—somatosensory. CARBON DIOXIDE—hypocarbia.

Changes in arterial carbon dioxide tension ($Paco_2$) are said to affect sensory evoked responses (SERs) (1). Accordingly, it has been recommended that acute changes in arterial blood gas tensions be avoided in order to facilitate accurate assessment of SERs during critical monitoring periods (2,3). Because the evidence for a substantial effect of low carbon dioxide tension on SERs is not well-documented, we undertook the following study to determine the influence of acute hypocapnia on human median nerve somatosensory evoked potentials (MnSSEPs).

Methods

This study was approved by the Committee on Investigations Involving Human Subjects of the University of California, San Diego. Each of the ten neurologically normal adult subjects (mean age 31.6 ± 11.9 yr) gave informed consent and was premedicated with morphine, 0.2 mg/kg intramuscularly, 60 min prior to induction of anesthesia. Under local anesthesia, an intravenous catheter was inserted in the forearm contralateral to the extremity to be stimulated for SSEP recording. Anesthesia was induced with thiopental, 4–8 mg/kg, and fentanyl, 10–15 μg/kg, and was maintained with a combination of nitrous oxide (65% inspired), isoflurane (0.5% inspired), and a nondepolarizing muscle relaxant. Total fresh gas flow was maintained at 9 L/min. The trachea was intubated, and the lungs were mechanically ventilated to maintain a normal end-tidal carbon dioxide tension ($ETco_2$), as measured by infrared absorption spectral analysis using an Expanded Performance CO_2 Monitor (Puritan Bennett Co., Overland Park, KS). Care was taken to calibrate and employ this instrument in strict observance of the manufacturer's guidelines.

SSEPs were recorded using a Pathfinder II Electrodiagnostic Monitoring System (Nicolet Biomedical, Madison, WI). The stimulation site over the median nerve at the wrist was identified with a bar-electrode stimulator (interelectrode distance = 3 cm). Adhesive electrodes were applied and the stimuli, which con-

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The opinions expressed herein are those of the authors and are not to be construed as reflecting the views of the Navy Department, the Naval Service at large, or the Department of Defense.

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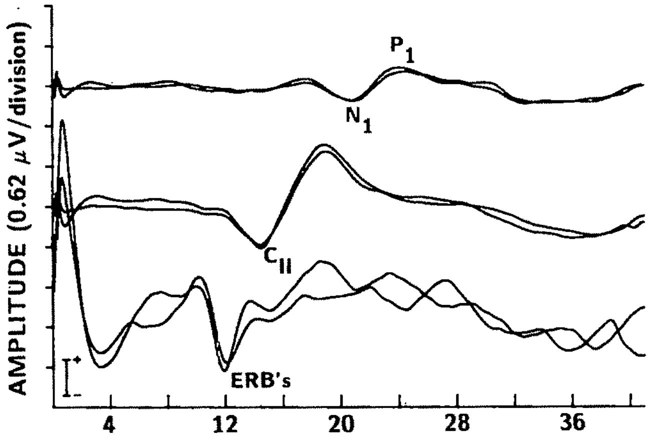

Figure 1. An example of reproducible MnSSEPs obtained from an anesthetized patient during normocapnia. Refer to text for full explanation of abbreviations.

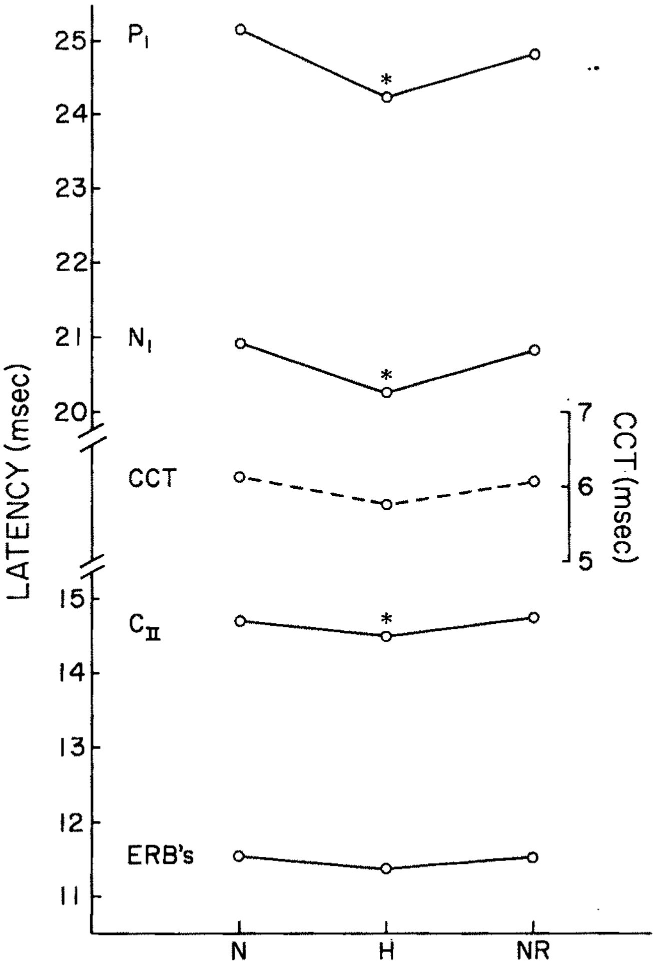

Figure 2. The effect of acute hypocapnia on MnSSEP latencies. Refer to text for full explanation of abbreviations.

sisted of 200 constant current impulses of 100 µsec in duration, were delivered at a rate of 3.1/sec. Stimulus intensity was adjusted to motor threshold plus 50%. To prevent local cooling, the stimulated extremity was wrapped.

SSEP waveforms were obtained simultaneously on three amplifier channels from recording electrodes (gold disk type, Grass Instruments) placed over the ipsilateral brachial plexus (Erb's point, channel 1), the spinous process of the second cervical vertebra (C_{II}, channel 2), and the contralateral sensory cortex (C_3' or C_4', channel 3), each referenced to FPz (International 10-20 system). The ground electrode was located over the mastoid process. Electrode impedances were maintained at less than 3 kΩ. The acquired signals were amplified 120,000 times (corresponding to a Pathfinder sensitivity setting of 50 µV). Bandpass filters were set at 30, and 250 Hz and a timebase of 40 msec following the stimulus was analyzed. All recordings were obtained in duplicate and compared for reproducibility. They were stored on magnetic disk for subsequent measurement of latency and amplitude using electronic cursors.

An example of a typical waveform acquired from an anesthetized normocarbic subject and analyzed in this manner is shown in Figure 1. The nominal negativities N9, N14, and N20 are referred to in this communication as Erb's (Point), C_{II}, and N_1 respectively, and the positive deflection immediately following N_1 as P_1. Amplitude measurements were made from each negativity to the succeeding positive waveform peak. In addition, a derived variable, the central conduction time (CCT), was calculated from the C_{II}–N_1 interwave latency.

Control SSEPs at normocapnia (N) were obtained approximately 20–25 min after induction when stable normocarbia (ETCO_2 37–40 mm Hg) had been maintained for 15 min. Hypocapnia (H) was then induced by mechanical hyperventilation and maintained at an ETCO_2 of 20–22 mm Hg for 15 min and repeat MnSSEPs were acquired under (H). ETCO_2 was then allowed to return to control level (38–41 mm Hg) by reducing minute ventilation. ETCO_2 was maintained at this level for 15 min, and the final MnSSEP (NR) was then recorded. No recordings were made earlier than 20 min after induction or surgical incision.

Each time that evoked responses were recorded, mean arterial pressure (MAP), heart rate (HR), nasopharyngeal temperature (NT), and ETCO_2 were recorded. A heater-humidifier, fluid warmer, and heating blanket were employed to keep NT constant. In two patients, measurement of blood gas tensions in a sample of venous forearm blood obtained without use of a tourniquet was also performed.

Table 1. Physiologic Variables

	Normocapnia (N)	Hypocapnia (H)	Return to normocapnia (NR)
ETCO_2 (mm Hg)	39.9 ± 1.4	20.6 ± 1.1	39.6 ± 1.2
MAP (mm Hg)	80.4 ± 15.5	84.8 ± 12.7	83.6 ± 13.4
HR (beats/min)	68.3 ± 13.6	68.8 ± 12.0	66.0 ± 11.9
NT (°C)	36.2 ± 0.6	36.2 ± 0.6	36.2 ± 0.6

All values are mean ± SD.

Abbreviations: ETCO_2, end-tidal carbon dioxide tension; MAP, mean arterial pressure; HR, heart rate; NT, nasopharyngeal temperature.

Table 2. Effect of Acute Hypocapnia on MnSSEP Latency (msec)

	Normocapnia (N)	Hypocapnia (H)	Return to normocapnia (NR)
Erb's	11.55 ± 0.72	11.38 ± 0.71	11.53 ± 0.90
C_{II}	14.80 ± 1.14	14.50 ± 1.13[a]	14.75 ± 1.08
N_1	20.93 ± 1.50	20.25 ± 1.49[a]	20.83 ± 1.44
P_1	25.17 ± 2.88	24.23 ± 2.52[a]	24.82 ± 3.04
CCT	6.14 ± 0.81	5.75 ± 0.61	6.07 ± 0.64

All values are mean ± SD.

[a] Significantly different ($P < 0.05$) from N.

Refer to text (p 241) for full explanation of abbreviations.

Statistical Analysis

The data obtained at N, H, and NR were subjected to a repeated measures analysis of variance. If a significant change was detected for a given set of measurements, pairwise comparisons were performed using the Bonferroni *t*-test with appropriate corrections for multiple comparisons.

Results

Values of MAP, HR, and NT did not change significantly throughout the study period (Table 1). The ETCO_2 during H averaged 20.6 ± 1.1 mm Hg, 19.3 mm Hg below that observed during N. This is consistent with the 20-mm Hg difference in venous PCO_2 measured in the two patients from whom blood samples were taken. Reproducible evoked response recordings were obtained at every measurement interval. Table 2 and Figure 2 show the latencies of the various SSEP components during N, H, and NR. Although there was a trend toward a decrease in the latencies of all SSEP components and CCT, only C_{II}, N_1, and P_1 latencies were significantly shorter during H when compared to N or NR. Mean decreases (± SD) in latency were 0.31 ± 0.23 msec, 0.68 ± 0.53 msec and 0.94 ± 0.65 msec, respectively. On return to N, latencies were not different from control measurements made during N. Cortical amplitude changes associated with H were variable, ranging from −40% to +34% for individual patients. However, with the exception of a small increase in C_{II} amplitude at H and NR, the alterations in the mean amplitude of SSEP components were not statistically significant (Table 3).

Discussion

Our results demonstrate that acute hyperventilation to an ETCO_2 of approximately 20 mm Hg consistently decreases MnSSEP latency by amounts less than one msec and that the effect on cortical amplitude is variable. The latter observation differs from the findings of Tachibana (1) who, in a study of the effects of stimulus intensity, nitrous oxide concentration, and mechanical hyperventilation on short latency MnSSEPs, noted a tendency for hyperventilated patients to respond with a smaller amplitude than those maintained at N. Latency was not studied. Group size was small (four patients each), and it is not clear how well other variables which may affect SSEPs, such as anesthetic state and temperature, were controlled. Also, statistical analysis of the SSEP differences between hypocapnic and normocapnic groups was not undertaken. The present results are therefore difficult to compare with those of Tachibana.

Chiappa (4) cites Larson et al. (5) as having observed that evoked potentials were independent of carbon dioxide tension until PaCO_2 decreased below 25 mm Hg. Unfortunately, little detail is available either about the magnitude of the observed response or the manner in which the observation was made by these investigators (5). Arterial carbon dioxide tension was not measured directly in our patients and was probably 2–6 mm Hg higher than the observed ETCO_2 of 20.6 ± 1.07 mm Hg (6,7). Accordingly, the degree of hypocapnia achieved in our study (estimated PaCO_2 = 23–27 mm Hg) probably did not greatly exceed the threshold for hypocapnia effects reported by Larson et al. Our data are thus consistent with their findings in the sense that, although we observed statistically significant decreases in latency at a PaCO_2 in the vicinity of 25 mm Hg, the magnitude of these changes was small and probably of little clinical significance.

The SSEP changes observed during hypocapnia were not likely to be due to factors other than those associated with the decrease in carbon dioxide tension. Specifically, MAP, HR, and NT remained constant at an acceptable level throughout the study period. In addition, while peripheral nerve injuries due to inappropriate positioning of patients have been shown

Table 3. Effect of Acute Hypocapnia on MnSSEP Amplitude (μV)

	Normocapnia (N)	Hypocapnia (H)	Return to normocapnia (NR)
Erb's	1.42 ± 0.90	1.52 ± 0.85	1.43 ± 0.83
C_{II}	1.83 ± 0.49	2.05 ± 0.55[a]	1.99 ± 0.60[a]
N_1–P_1	0.89 ± 0.42	0.87 ± 0.36	0.73 ± 0.42

All values are mean ± SD.
[a] Significantly different ($P < 0.05$) from N.
Refer to text (p 241) for full explanation of abbreviations.

to affect SSEPs, our patients remained in the same position throughout the study and care was taken to avoid extreme head rotation and arm abduction.

Changes in the anesthetic state could conceivably have contributed to the SSEP alterations we observed. Specifically, diminishing plasma levels of intravenous anesthetics after bolus administration of intravenous induction agents or changing arterial inhaled anesthetic concentrations during hyperventilation might have had an influence. In order to minimize the effect of rapidly decreasing plasma thiopental and fentanyl levels, the initial normocapnic recordings were delayed for at least 20 min after induction.

Under nonsteady-state conditions, increasing minute ventilation can enhance delivery of inhaled anesthetic with a resultant increase in the rate of increase of alveolar concentrations. In our patients, inspired N_2O and isoflurane concentrations as well as the level of mechanical ventilation were kept constant for at least 25 min prior to the start of hyperventilation, suggesting that near steady-state conditions should have been attained. Had this not been the case, hyperventilation-induced increased anesthetic delivery combined with decreased uptake (through a reduction in cardiac output) would be expected to produce a more rapid increase in the arterial inhaled anesthetic concentration. This should result in a lengthening, rather than a shortening of SSEP latencies (8). Thus the H-induced decrease in SSEP latency observed in this study conceivably would have been more prominent had hyperventilation-related changes in anesthetic level been excluded. However, in all probability our patients were well-equilibrated with the inspired gas mixture prior to the initial SSEP recordings, and it is unlikely that changing concentrations of inhaled agents made a significant contribution. Measurement made during normocapnia (N) after the period of hypocapnia (H) in our study (NR) provided a means for evaluation of factors not related to hyperventilation per se. Thus the absence of SSEP changes between N and NR, as well as the constancy of HR and MAP during the study period, speak against the likelihood that changing anesthetic levels had a significant influence on the data which were obtained.

The mechanisms involved in the shortening of SSEP latencies during hypocapnia must remain a matter of speculation. Hyperventilation may have augmented nerve excitability and conduction velocity (thus accounting for the shorter SSEP latencies) as a result of effects on ionized calcium levels. Alkalosis is widely known to reduce serum ionized calcium levels through increased protein binding and studies in vitro and in vivo have demonstrated increased excitability in nerves exposed to solutions of low calcium concentration (9,10). Transient improvement of symptoms of multiple sclerosis as a result of measures that reduce serum ionized calcium has also been attributed to hypocalcemia-related restoration of conduction in blocked demyelinated nerve fibers and to improvement of conduction in functioning fibers (11–13). Aside from its effect on ionized serum calcium hyperventilation may also enhance nerve excitability separately through direct effects of decreased $Pa\text{CO}_2$ (14) and hydrogen ion concentration (15).

In summary, the present study demonstrates that only minor decreases (< 1 msec) in MnSSEP latencies occur during acute hypocapnia. Cortical latencies were affected to a greater extent than subcortical ones. The effect on cortical amplitude was variable. The authors conclude that the MnSSEP can be consistently and reliably recorded during acute hypocapnia to an $ET\text{CO}_2$ of 20 mm Hg (estimated $Pa\text{CO}_2$ = 23–27 mm Hg), and that hypocapnia-induced alteration of MnSSEP waveforms is unlikely to interfere with clinical interpretation of SSEP changes.

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Disposition and Urinary Excretion of Vecuronium Bromide in Anesthetized Patients with Normal Renal Function or Renal Failure

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BENCINI AF, SCAF AHJ, SOHN YJ, MEISTELMAN C, LIENHART A, KERSTEN UW, SCHWARZ S, AGOSTON S. Disposition and urinary excretion of vecuronium bromide in anesthetized patients with normal renal function or renal failure. Anesth Analg 1986;65:245–51.

The effect and plasma concentrations of vecuronium bromide were measured in normal patients after an intravenous dose of 50, 100, or 150 μg/kg and in patients with renal failure after 50 or 100 μg/kg. Urinary excretion of vecuronium was studied in normal patients after the 150 μg/kg dose. Pharmacokinetic parameters of patients with or without renal failure were similar. No metabolites of vecuronium were found in the plasma. Twenty percent of vecuronium was excreted unchanged in the urine; 5% as the 3-hydroxy derivative. No other metabolites of vecuronium were found in the urine. Increasing doses of vecuronium shortened the onset, but prolonged the duration of action and the recovery rate, to a similar extent in patients with or without renal failure. It was concluded that the disposition of vecuronium was best described by a three compartment model. Both the disposition and the effect of vecuronium are only marginally disturbed by renal failure.

Key Words: NEUROMUSCULAR RELAXANTS—vecuronium.

In contrast to its bisquaternary homologue, pancuronium bromide, vecuronium bromide has a relatively short duration of action and less cumulative effects in patients with normal renal function (1–4) as well as in patients with renal failure (5). These desirable characteristics can be explained by a total clearance rate that is, with the exception of atracurium (6), faster than that of other nondepolarizing neuromuscular blocking agents (7).

Urinary excretion of vecuronium probably contributes only slightly to this sizeable clearance, because neither the pharmacodynamic nor the pharmacokinetic behavior of vecuronium differs significantly in patients with renal failure or patients with normal kidney function (8). However, in the only study performed in patients with renal failure the assay method used (high performance liquid chromatography) lacked the sensitivity required for this type of study (limit of detection 50 ng/ml). Moreover, no clinical study published so far has actually measured the amount of vecuronium excreted in the urine, although studies in the rat demonstrated that only about 3.5% of an injected dose of vecuronium is eliminated in the urine (9).

We have therefore investigated the pharmacokinetics of vecuronium bromide in patients with normal renal function or with renal failure, using a more sensitive and specific sequence of fluorimetric (limit of detection 10 ng/ml) and chromatographic analysis. In addition, the amounts of vecuronium and its metabolites excreted in the urine were measured, and the recovery from neuromuscular block was correlated with the plasma concentration.

Methods

Patient Selection

This study was approved by the Ethics Committees of the University Hospital of Groningen and the C.H.U. Pitié Salpêtrière in Paris. All patients gave their informed consent to participate in the study at the preoperative visit.

The 37 male or female patients aged 20–50 yr were

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Table 1. Kinetic Macroparameters of Plasma Curves

	Normal 50 μg·kg^{-1} (n = 6)	Renal failure 50 μg·kg^{-1} (n = 8)	Normal 100 μg·kg^{-1} (n = 7)	Renal failure 100 μg·kg^{-1} (n = 8)	Normal 150 μg·kg^{-1} (n = 6)
C_1 (μg·ml^{-1})	0.74 (68%)	0.64 (62%)	1.33 (77%)	1.05 (83%)	1.30 (33%)
C_2	—	—	0.47 (65%)^a	0.46 (52%)	0.77 (90%)^a
C_3	0.16 (75%)^b	0.07 (69%)^b	0.07 (80%)	0.09 (112%)	0.04 (98%)
λ_1 (hr^{-1})	15.18 ± 9	15.6 ± 13.8	34.14 ± 18.4	25.08 ± 23.6	30.42 ± 30.4
λ_2	—	—	4.25 ± 1.8	2.74 ± 0.9	3.13 ± 1.4
λ_3	1.29 ± 1.4	0.58 ± 0.3	0.35 ± 0.3	0.28 ± 0.2	0.39 ± 0.3
$(t_{1/2})_1$ (min)	2.74	2.63	1.22	1.66	1.37
$(t_{1/2})_2$	—	—	9.80	15.21	13.31
$(t_{1/2})_3$	34.11	71.32	117.00	149.00	108.00
V_1 (ml·kg^{-1})	—	—	42 ± 25	53.80 ± 32.11	76 ± 68
V_d^{ss} (ml·kg^{-1})	—	—	510 ± 296	471 ± 355	413 ± 367
Cl (ml·min^{-1}·kg^{-1})	—	—	3.18 ± 0.21	2.57 ± 0.31	4.58 ± 0.65

[a,b] Significant differences between similarly marked groups ($P \leq 0.05$, Wilcoxon rank sum test).

C_1–C_3 are the intercepts on the y-axis at time 0 of the component exponential curves (denoted by suffix 1, 2, 3) making up the plasma concentration decay curve. λ_1–λ_3 are the rate constants describing the rate of decline of the component exponential curves making up the plasma concentration decay curve. $(t_{1/2})_1$–$(t_{1/2})_3$ are the half-lives of the component exponential curves and are another way of describing the rate of decline of these curves. V_1 is the apparent volume of distribution of the central department (compartment 1) of the kinetic model. V_d^{ss} is the apparent volume of distribution of steady state. Cl is the total body clearance. Because plasma curves were analyzed on a semi-log scale, intercepts (C_1–C_2) are presented as mean (% coefficient of variation). All other data are presented as mean ± SD. Half-lives ($t_{1/2}$) are derived from the mean of the rate constants (λ) according to the equation $t_{1/2} = \frac{0.693}{\lambda}$; therefore no SD is given here.

allocated to five groups as shown in Table 1. Overweight patients were excluded from the investigation. Patients with normal renal function were eligible for the study if classified as ASA I or II. Patients were considered to be in renal failure if they had a renal creatinine clearance of less than 5 ml/min; most of these patients had just been hemodialyzed before presenting for operation. Anephric patients whose general condition was worse than ASA III were not accepted for this study. All patients with renal failure underwent operations to establish arterio–venous fistula. No patients who came in for renal transplantation were accepted for this study because newly transplanted kidneys have been shown to be capable of excreting some neuromuscular blocking agents, e.g., *d*-tubocurarine (10). Only patients who underwent operations that did not require transfusions of large amounts of fluid (more than 50% of the total blood volume) were investigated.

Anesthesia

Patients were premedicated with droperidol, 0.15 mg/kg intramuscularly, together with atropine, 8–10 μg/kg intramuscularly, 1 hr before induction of anesthesia. Anesthesia was then induced with thiopental, 3–5 mg/kg, followed by fentanyl, 2 μg/kg, and 66% nitrous oxide oxygen. Tracheal intubation was facilitated with succinylcholine in patients given vecuronium, 100 or 150 μg/kg. Anesthesia was maintained by supplementation with fentanyl, to a total of 5–10 μg/kg, together with 0.5% halothane. Controlled ventilation was established, and the end-tidal CO_2 remained between 4–5 kPa. Esophageal temperature was maintained at ±37°C by means of a warming mattress and warmed inspired anesthetic gases. Perioperative fluid balance was maintained with dextrose-saline solution (4.75–0.18%) at an average infusion rate of 4 or 2 ml·kg·$^{-1}$hr^{-1} in normal patients or anephric patients, respectively.

Experimental Procedure

The design of the experiment is illustrated in Figure 1. Using a Myotest nerve stimulator (11), the ulnar nerve was stimulated at the wrist through percutaneous electrodes. The adduction force of the resulting thumb twitch was measured with a displacement transducer (Statham UC3, gold cell) and recorded on a Gould Brush 220 recorder. Single, square-wave, electrical impulses of 0.2-msec duration were applied to the nerve every 10 sec. Monitoring of neuromuscular function was begun immediately after induction of anesthesia and continued until the twitch height had maximally recovered. Vecuronium bromide was administered, over 2 min, in a dose of 50 (n = 16), 100 (n = 15), or 150 μg/kg (n = 6) dissolved in 10 ml of sterile saline solution.

Blood was drawn from a peripheral vein in the arm opposite to that used for infusion of drugs. Eight milliliters of blood was collected several minutes before the injection of the muscle relaxant (blank sample)

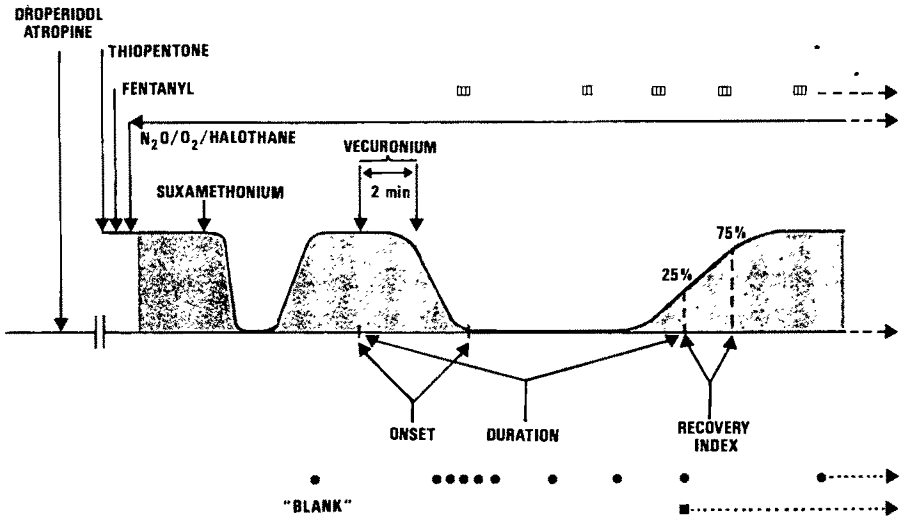

Figure 1. Experimental design. Symbols: ▥, fentanyl maintenance doses; ●, blood samples; ■, urine samples. Shaded areas denote course of neuromuscular blockade.

and at 1, 3, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, and 300 min after injection of vecuronium. To prevent degradation of vecuronium, all blood samples were buffered with 2 ml of 1M disodium hydrogen phosphate, centrifuged, and deep frozen to −30°C to await further analysis.

Urine was collected from five of the patients who received 150 μg/kg via an indwelling urinary catheter 1, 2, 3, 4, 5, 6, 12, 18, and 24 hr after the injection of the vecuronium. The amount of urine excreted during each period, collected in a bag, was noted, and an 8-ml sample was obtained from each lot of urine. This was buffered with 2 ml of 1M disodium hydrogen phosphate and deep frozen until analysis.

Chemical Analysis

The total amount of vecuronium (including its metabolites) in the blood and urine samples was measured by a modification of the fluorimetric technique described for pancuronium by Kersten et al. (12). (This technique does not separately measure the various amounts of vecuronium or its metabolites.) The coefficient of variation of this technique is 3–10% in the 5–100 ng/ml range. The amount of unchanged vecuronium and its three putative metabolites, namely the 3-hydroxy, the 17-hydroxy, and the 3,17-dihydroxy derivatives (13) in every sample was then measured by means of thin-layer plate chromatography. In this technique the amount of each compound is assessed by visual comparison of the spot size and density with those produced by known amounts of reference compounds. The coefficient of variation of this method is ±10%, and as little as 150 ng of compound can be detected.

Pharmacokinetic Analysis

Multiexponential equations of up to five exponential terms were fitted to the experimental plasma concentration decay curves by means of a computer program (RUGFIT) written by one of the authors (AHJS). This program carries out, by means of linear least square regression, reiterative peeling of the experimental decay curves plotted on a semilogarithmic scale. The number of exponential terms that described the experimental plasma concentration decline was selected according to the criteria described by Boxenbaum et al. (14).

Statistical Analysis

The Wilcoxon rank sum test was applied to determine the statistical significance of differences between results in the various groups of patients. A value of $P < 0.05$ was considered to be statistically significant.

Results

Plasma Concentrations after Different Doses in Normal Patients

The decline of the plasma concentration of vecuronium after 50, 100, or 150 μg/kg intravenously in normal patients is shown in Figure 2; the parameters that describe these curves are listed in Table 1 (first, third, and fifth columns from the left).

The curve obtained with the 50 μg/kg dose is short because the plasma concentration of vecuronium rapidly decreased to undetectable concentrations (Fig. 2). The curve obtained after 50 μg/kg of vecuronium was

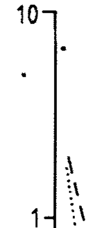

Figure 2. Mean plasma concentration decay curve of vecuronium in patients with normal renal function after 50 (n = 8), 100 (n = 7), and 150 µg/kg (n = 6). Horizontal bars on curves denote mean concentration at 25% (higher bar) and 75% (lower bar) recovery of twitch height. These concentrations were not measured in patients given 50 µg/kg.

best described by a biexponential function, in contrast to the other two curves (after 100 or 150 µg/kg) that, in the majority of patients, could be best resolved into three exponential terms (Table 1). Because the curves obtained after the 50-µg/kg dose are so short, they were not analyzed further than the intercepts and rate constants and will not be considered anymore in this study. The parameters derived from the plasma curves obtained after 100 and 150 µg/kg (Table 1) do not show any significant difference from each other except for the intercept of the second distribution phase (C_2).

In Figure 2, the mean plasma concentrations corresponding to 25 and 75% recovery of the twitch are shown as short bars bisecting the respective curves. These concentrations are also listed in Table 2. Only the values for the 100- and 150-µg/kg curves were measured; they showed no significant differences from each other. None of the three putative metabolites of vecuronium were detected in the plasma of these patients.

Plasma Concentrations in Patients with Renal Failure

Figure 3 shows the decline of the plasma concentrations of vecuronium after an intravenous injection of 100 µg/kg in patients with normal renal function as well as in anephric patients. The corresponding parameters of these two curves are compared in columns 3 and 4 of Table 1, respectively.

In contrast to normal patients, vecuronium disappears from the plasma of patients with renal failure somewhat more slowly—during all three phases of the decay curve. This results in a curve that runs above the curve obtained from patients with normal renal function.

As mentioned before, the bars bisecting the curves in Figure 3 denote the concentrations of vecuronium in the plasma when the twitch height has recovered to 25 and 75% of control, respectively. In patients with renal failure, recovery of the twitch height correlates with a significantly higher concentration of vecuronium in the plasma. None of the metabolites of vecuronium were detected in the plasma of patients with renal failure.

Urinary Excretion of Vecuronium

The cumulative urinary excretion of vecuronium and its metabolites is shown in Figure 4.

Table 2. Plasma Concentrations of Vecuronium at 25% and 75% Recovery of the Twitch Height

Vecuronium dose (µg/kg intravenous)	Concentration at 25% recovery (µg/ml)		Concentration at 75% recovery (µg/ml)	
	np	rf	np	rf
100	0.13 ± 0.02[a] (n = 4)	0.21 ± 0.06[a] (n = 7)	0.07 ± 0.03[b] (n = 4)	0.15 ± 0.05[b] (n = 7)
150	0.13 ± 0.01 (n = 6)	—	0.08 ± 0.02 (n = 6)	—

[a,b] Significant differences between similarly marked groups ($P < 0.05$).
np, Normal patients; rf, renal failure patients; n, number of patients in group. All values mean ± SD.

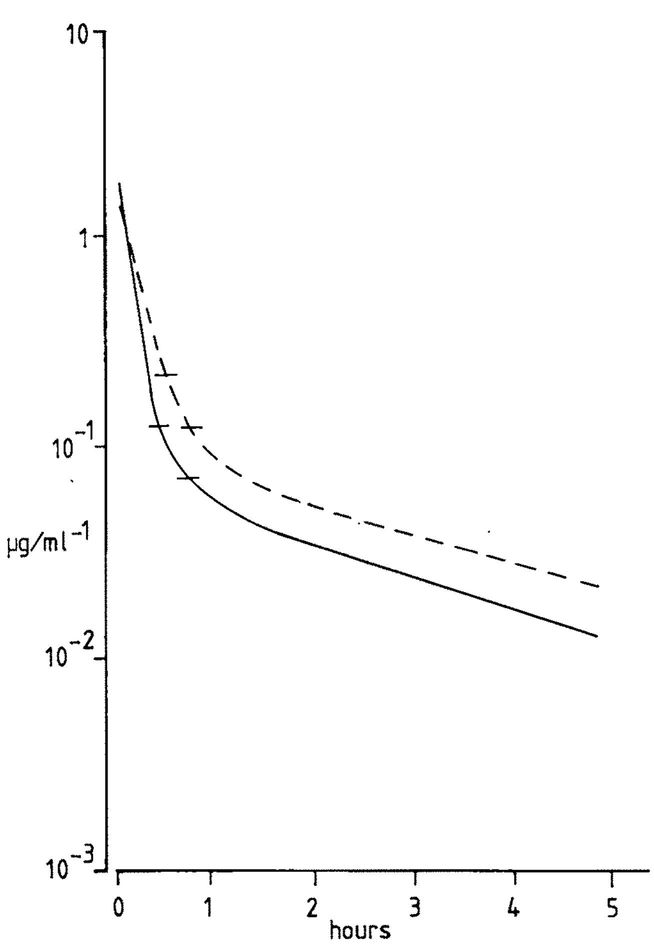

Figure 3. Mean plasma concentration decay curves of vecuronium in 7 normal patients (——) and 8 patients with renal failure (---) after 100 μg/kg of vecuronium. Horizontal bars bisecting curves denote mean concentration at 25% (higher bar) and 75% (lower bar) recovery of twitch height.

After 150 μ/kg of vecuronium, the total amount of monoquaternary compounds excreted in the urine at the end of 24 hr was a little more than 30% of the injected dose. Ten percent of this total was excreted as the 3-deacetyl-vecuronium (3-OH metabolite). None of the other two metabolites of vecuronium, namely the 17-hydroxy and the 3,17-dihydroxy metabolites, were detected in the urine.

Neuromuscular Blocking Effects of Vecuronium

The neuromuscular blocking effects of vecuronium in normal and anephric patients, after the three doses used in this study, are summarized in Table 3. Because vecuronium was administered as a 2-min infusion, the onset time to maximum block was calculated from the start of the injection.

Discussion

It is evident in this study that for proper pharmacokinetic analysis a sufficiently long plasma concentration decay curve is required. This is only possible if a sensitive assay method is used. The curve obtained after the 50-μg/kg dose is short because the plasma concentration of vecuronium quickly decreases below detectable levels. Consequently, the third phase of the decline of vecuronium plasma concentration, seen in the curves obtained after the larger doses of vecuronium, is almost entirely missed. As a result, the curve obtained after 50 μg/kg of vecuronium is best described by a biexponential function, in contrast to the other two curves (after 100 and 150 μg/kg of ve-

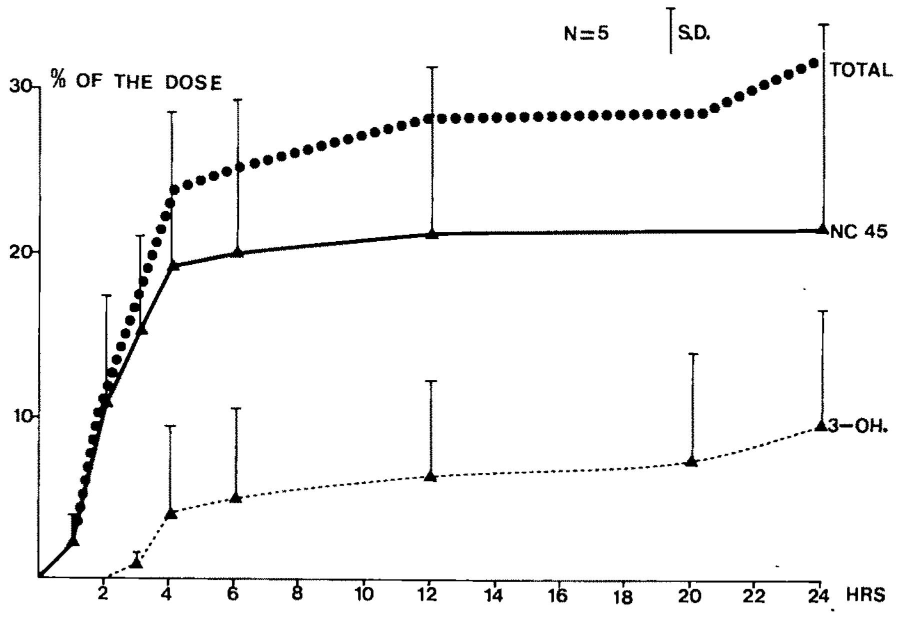

Figure 4. Cumulative urinary excretion of vecuronium and its 3-hydroxy derivative (3-OH) in 5 normal patients after 150 μg/kg. SD, standard deviation.

Table 3. Neuromuscular Blocking Effects of Vecuronium Bromide

Intravenous dose (μg/kg)	n	Onset (min)		Maximum block (%)		Duration to 25% recovery (min)		Recovery rate 25–75% (min)	
		np	rf	np	rf	np	rf	np	rf
50	10	5.9 ± 2.5	5.2 ± 2.3	93 ± 12	91 ± 7.1	18.1 ± 6.6^{a}	22.3 ± 7.0^{b}	7.2 ± 3.1	10.5 ± 3.6^{c}
100	7	2.9 ± 0.3^{d}	5.1 ± 1.2^{d}	100	100	23.6 ± 9.3^{a}	29.6 ± 4.2^{b}	8.8 ± 1.0^{e,f}	17.2 ± 1.0^{c}
150	7	2.7 ± 0.4	—	100	—	41.8 ± 9.4^{a}	—	11.9 ± 3.1^{f}	—

^{a,b,c,d,e,f}Significant differences between similarly marked groups ($P < 0.5$).
np, Normal patients; rf, renal failure patients. All values mean ± SD.

curonium), that are best resolved into three exponential terms.

Similarly, early kinetic studies of vecuronium in dogs (15) and humans (16) suffered from too short a plasma concentration decay curve. This problem was a direct consequence of the relative insensitivity of the assay method used in those studies (high performance liquid chromatography), which can detect vecuronium concentrations only above 50 ng/ml (17). This problem was overcome by Fahey et al. (8), who also used the high performance liquid chromatography method, by resorting to the administration of a large dose of vecuronium (0.28 mg/kg, five times the recommended ED_{90} dose). But this in itself can lead to faulty results, as large doses of a drug can, in principle, lead to nonlinear pharmacokinetic processes with a consequent shallow rate of decay in the early phases of plasma concentration decline. Perhaps for this reason, although they could follow the plasma decay curve for several hours after injection, Fahey et al. selected a biexponential function to describe the plasma decay curve of vecuronium. It is interesting to note that other authors (18) who have applied mass spectrometry to the measurement of vecuronium concentration (lower limit of detection 2 ng/ml) found that the disposition kinetics of vecuronium could be best described by a model with three compartments and with pharmacokinetic parameters that agree closely with those generated in this study. Because mass spectrometry is both the most sensitive assay method available to date, and because it specifically measures only unchanged vecuronium (or any of its metabolites, if so desired) we feel that vecuronium disposition kinetics are best described by a three-compartment model.

It is shown in this study that anephric patients who received 100 μg/kg had significantly higher plasma concentration at 25 and 75% recovery than patients without renal failure. This surprising apparent tolerance to vecuronium in patients with renal failure is further supported by a tendency to a slower onset of action in these patients (Table 3). Other workers (5) have also brought forward some evidence that this phenomenon may indeed occur with both vecuronium and, to a lesser extent, atracurium. Whether this is true, or whether other nondepolarizing muscle relaxants generally show this characteristic, remains ambiguous. Thus, though Brotherton and Matteo (19) suggest that individuals with renal failure have a decreased sensitivity to metocurine, other workers report that neuromuscular sensitivity to gallamine (20) and *d*-tubocurarine (10) is not altered in patients with renal failure.

This study provides conclusive evidence for the assumption of other investigators that, as in the rat (9), only moderate amounts of vecuronium are eliminated by the kidneys (8). Accordingly, patients with renal failure show only a slightly delayed removal of vecuronium from the plasma with, consequently, only mild prolongation of effect and recovery. This prediction is supported by Hunter et al. (5), who found little cumulative effect with comparable doses in anephric patients who were administered up to six maintenance doses, each of 40 μg/kg. We agree, therefore, with these and other authors (4,21) that vecuronium is suited for use in patients with renal failure.

In summary, the disposition of vecuronium is best described by a three-compartment pharmacokinetic model. Moreover, only moderate amounts of vecuronium are excreted by the kidney, and only mild alteration of pharmacokinetic and pharmacodynamic behavior of vecuronium occurs in patients with renal failure. Vecuronium is, therefore, suitable for use in patients with renal failure.

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Effects of Dantrolene and Verapamil on Atrioventricular Conduction and Cardiovascular Performance in Dogs

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LYNCH C III, DURBIN CG Jr, FISHER NA, VESELIS RA, ALTHAUS JS. Effects of dantroline and verapamil on atrioventricular conduction and cardiovascular performance in dogs. Anesth Analg 1986;65:252–8.

The effects of intravenous dantrolene sodium, alone and in combination with verapamil, upon atrioventricular conduction, cardiovascular function, and neuromuscular function were studied in chloralose–urethane anesthetized dogs. Hemodynamic variables (systemic arterial, central venous, and pulmonary arterial pressures and cardiac output) and His-bundle electrograms were monitored, and measurements were made during atrial pacing at 175 beats/min, as well as at the spontaneous heart rate. In one part of the study animals received dantrolene sodium incrementally at 30-min intervals to cumulative doses of 1, 2.5, 5, and 10 mg/kg. Subsequently, verapamil was administered incrementally at 30-min intervals to cumulative doses of 0.1, 0.2, 0.4, and 0.6 mg/kg. In the second part of the study, dogs received identical dosage sequences, but verapamil preceded dantrolene administration. Dantrolene caused no significant depression of atrioventricular conduction or cardiac performance but did increase systemic vascular resistance at doses above 2.5 mg/kg. Verapamil alone (≥ 0.2 mg/kg) or with dantrolene (≥ 0.1 mg/kg) increased the atrial–His-bundle conduction interval. In the presence of verapamil, dantrolene (≥ 2.5 mg/kg) decreased cardiac index and increased pulmonary artery occlusion pressure. Although 0.6 mg/kg verapamil depressed cardiac index and increased pulmonary artery occlusion pressure, this effect was observed at 0.4 mg/kg after prior treatment with dantrolene. Verapamil did not augment the dose-dependent twitch depression observed with dantrolene. Dantrolene alone had no apparent effect on atrioventricular conduction and caused little enhancement of the effects of verapamil. However, each drug appeared to enhance the myocardial depressant effects of the other.

Key Words: PHARMACOLOGY—verapamil, dantrolene. HEART—atrioventricular, conduction, myocardial function. NEUROMUSCULAR RELAXANTS—dantrolene.

Dantrolene sodium, which interferes with the release of calcium from the sarcoplasmic reticulum of skeletal muscle, and thereby inhibits excitation–contraction coupling (1,2), is the pharmacologic treatment of choice for malignant hyperpyrexia (3,4), as well as certain spastic disorders of skeletal muscle (5). Dantrolene is reported to have no significant hemodynamic effects in intact animals (6,7) but can depress myocardial contractility in isolated myocardial tissue (8–10). Dantrolene has been noted to have a verapamil-like effect in depressing calcium-dependent slow action potentials in Purkinje fibers (8). Because the initiation of the cardiac impulse in the sinoatrial node and conduction through the atrioventricular (A-V) node is mediated by calcium-dependent slow action potentials, and depressed by calcium entry blockers (11), we examined the effects of dantrolene upon cardiac conduction.

Calcium entry blockers have also been suggested as a pharmacologic treatment for malignant hyperpyrexia, either alone or in combination with dantrolene (12,13). Verapamil is well known to depress cardiac conduction through A-V nodal tissue as well as depressing the spontaneous rate of sinoatrial nodal impulses (11,14–16). In view of the potential for marked depression of A-V conduction or myocardial function by the combination of dantrolene and verapamil, we also studied the effects of these drugs in combination. Preliminary results have been previously reported (17).

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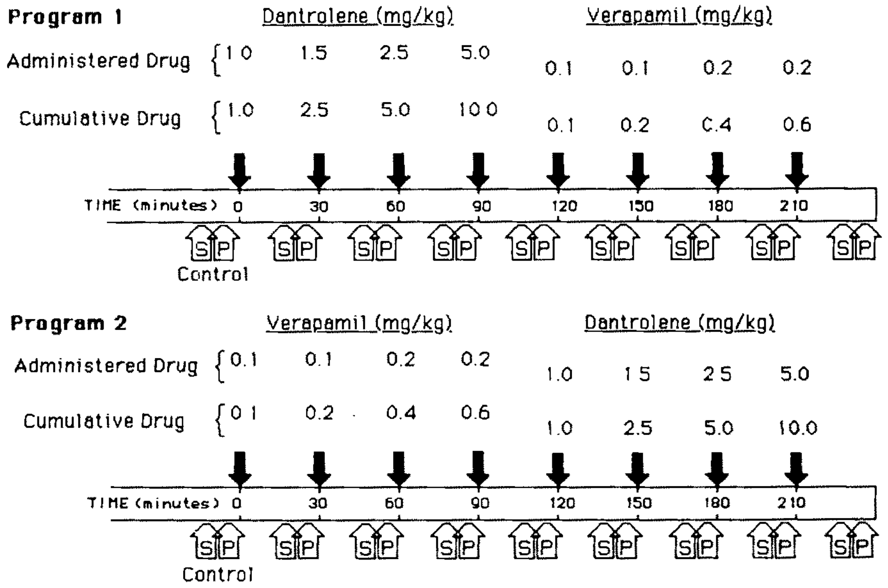
Program 1
Dantrolene (mg/kg)
Verapamil (mg/kg)
Administered Drug {1.0 1.5 2.5 5.0 0.1 0.1 0.2 0.2
Cumulative Drug {1.0 2.5 5.0 10.0 0.1 0.2 0.4 0.6
TIME (minutes) 0 30 60 90 120 150 180 210
S P
Control
Program 2
Verapamil (mg/kg)
Dantrolene (mg/kg)
Administered Drug {0.1 0.1 0.2 0.2 1.0 1.5 2.5 5.0
Cumulative Drug {0.1 0.2 0.4 0.6 1.0 2.5 5.0 10.0
TIME (minutes) 0 30 60 90 120 150 180 210
S P
Control

Figure 1. Sequence of events in the two drug programs employed. The incremental intravenous dose administered is indicated by the filled arrows; the total cumulative dose is also indicated above each time line. Atrioventricular condition and hemodynamic measurements, either during spontaneous rhythm (S) or pacing (P), were made at approximately the time indicated by the unfilled arrows.

Methods

Twelve mongrel dogs weighing 18.8 ± 3.8 kg (± SD), verified to be free of heart worms by autopsy or serological testing, were studied after premedication with 100 mg of pentobarbital and 10 mg morphine. After intubation of the trachea, the animals were maintained on mechanical ventilation with 30% O_2 and 70% N_2. Periodic sampling of blood gases confirmed the Pa_{CO_2} to be 35–45 mm Hg. Anesthesia was maintained with incremental doses of α-chloralose (40–80 mg/kg) and urethane (400–800 mg/kg). Temperature was maintained at 36–37.5°C by application of heating lamps as required.

In addition to intravenous access and catheterization of the bladder, the femoral artery was cannulated for direct monitoring of systemic arterial pressure and access for blood sampling. A 7-French thermodilution Swan–Ganz pulmonary artery catheter (American Edwards Laboratories) was introduced through the femoral vein to the pulmonary artery to measure mean central venous pressure (CBP), pulmonary arterial pressure (PAP), and mean pulmonary artery occlusion pressure (PAOP), as well as core temperature and cardiac output (CO) (Edwards 9520A Computer). Pressures were transduced with Statham P23 transducers and recorded on a Gould 4200 HL recorder. Cardiovascular variables were measured at end expiration, and cardiac output was determined from the average of a minimum of three measurements. To assess neuromuscular function, extensor twitch tension in the right hind limb was monitored by a Grass FT10 transducer. Twitches were elicited by supramaximal stimulation at 0.1 Hz (Grass S88 stimulator) of the posterior tibial nerve by needle electrodes.

After surgical exposure, a quadripolar Castillo catheter was advanced from the left carotid artery to the noncoronary cusp of the aortic valve (18) and the His-bundle electrogram recorded at 100 mm/sec. Atrial–His-bundle (AH) and His-bundle–ventricular (HV) intervals were then measured from this recording. After exposure of the right internal jugular vein, a 5F balloon-directed pacing catheter (Electro-catheter Corporation) was placed in the right atrium, and pacing was achieved with a Grass S44 stimulator (0.5 msec stimuli of twice threshold magnitude).

After a stabilization period of 1 hr, control measurements were made. Six animals were randomly assigned to one of two programs, diagrammed in Figure 1. An intravenous dantrolene dose of 1 mg/kg was administered, and at 30-min intervals additional dantrolene doses of 1.5, 2.5, and 5.0 mg/kg were consecutively administered to give cumulative doses of 2.5, 5.0, and 10 mg/kg. Verapamil, 0.1 mg/kg, was administered intravenously 30 min after the last dose of dantrolene. Subsequent doses of 0.1, 0.2, and 0.2 mg/kg of verapamil were administered at 30-min intervals for total cumulative verapamil doses of 0.2, 0.4, and 0.6 mg/kg. In the second part of the study, verapamil was administered prior to dantrolene. Dantrolene was administered in a solution that contained 0.5 mg dantrolene sodium and 44 mg mannitol per ml at a rate of 20 cc/min. The total maximum volume load was 20 ml/kg of water and 0.88 mg/kg mannitol. A brisk diuresis usually followed dantrolene administration. Intravenous fluids were administered as required to maintain the central venous pressure at 4–7 mm Hg.

Hemodynamic measurements were recorded continuously during spontaneous cardiac rhythm. In most experiments, His-bundle electrograms were recorded during the peak hemodynamic effects of verapamil and at 10 and 20 min after the drug administration. In the case of dantrolene, recordings were made at approximately 10 min after the beginning of drug administration, which took 1–12 min depending on dose, and about 20 min after initiation of dosage. Results tabulated and presented are for measurements made after approximately 20 min. At 23–25 min after drug administration, cardiac pacing was begun and measurements made after at least 1 min, during which occasional small hemodynamic changes had stabilized. Each animal was always paced at the same rate during the experimental period, which was approximately 20 beats/min greater than the spontaneous rate during the control period (usually 145 to 160 beats/min). Pacing rate averaged 175 ± 7 (± SEM) beats/min in all animals studied. When the animals were paced, the atrial His-bundle interval was measured from the stimulus artifact to the His-bundle deflection, in order to improve accuracy.

In order to ensure that appropriate drug levels were achieved, a later series of experiments was performed in which six additional dogs (three in each experimental program) were studied, but without His-bundle electrogram recording or pacing. Serum samples were obtained just prior to experimental measurements. Dantrolene concentration was determined according to the method of Hackett and Dusci (19), employing high-performance liquid chromatographic (HPLC) separation and fluorescence detection. Verapamil concentration was measured by the method of Watson and Kapur (20), employing HPLC separation and fluorescence detection.

Due to the intrinsic variability among animals, the change from control for each variable in each animal was determined and statistically analyzed. Significance ($P < 0.05$) of change from control was tested by analysis of covariance. Difference between program groups was examined by a general linear models procedure employing Duncan's multiple range test.

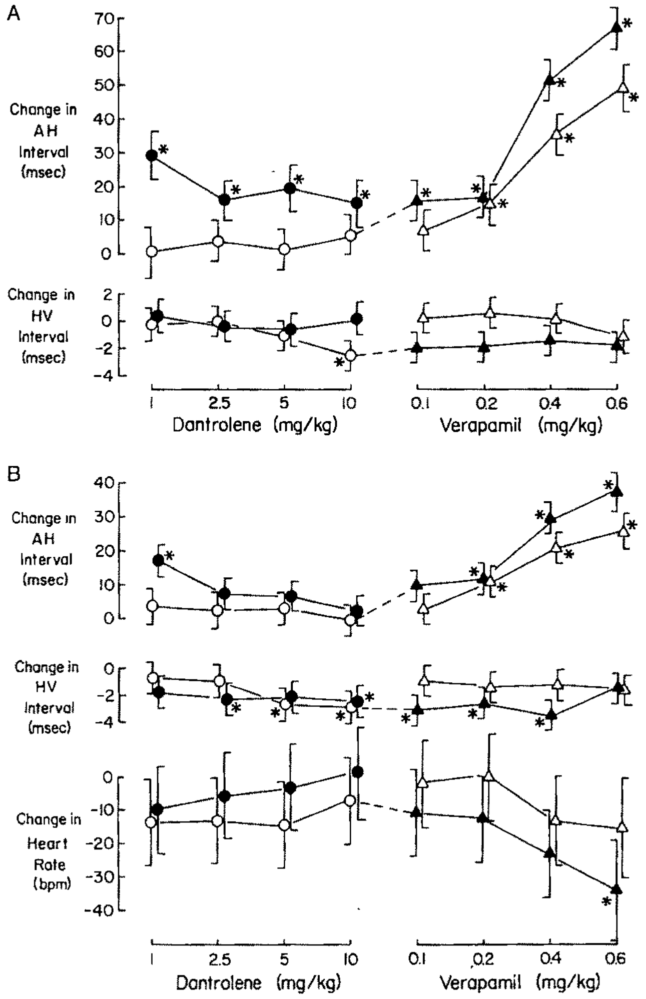

Figure 2. Changes in atrial–His-bundle (AH) interval and His-bundle–ventricular (HV) interval with incremental doses of dantrolene and verapamil. Each point represents the average of six animals studied, and the vertical axis indicates the average change from control for the dosage indicated on the horizontal axis. The error bar is the standard error of the average change from control. Values plotted are for the following: dantrolene alone, program 1 (○); dantrolene after earlier verapamil administration, program 2 (●); verapamil alone, program 2 (△); and verapamil after earlier dantrolene administration, program 1 (▲). *indicates a change from control of significance ($P < 0.05$) by analysis of covariance. There was no significant difference in the control values between program groups. (A) Changes in AH and HV intervals in animals paced at a constant heart rate, which averaged 175 ± 7 beats/min in the animals studied. The AH interval was measured from the stimulus artifact to the His-bundle deflection. The average (± SEM) control AH intervals were 80 ± 5 msec (program 1) and 91 ± 5 msec (program 2). The average control HV intervals were 29 ± 2 msec (program 1) and 25 ± 2 msec (program 2). (B) Changes in AH and HV intervals and heart rate in animals without pacing. The average control values were the following: heart rate, 158 ± 15 beats/min (program 1) and 153 ± 13 beats/min (program 2); AH interval, 73 ± 2 msec (program 1) and 79 ± 4 msec (program 2); HV interval, 29 ± 2 msec (program 1) and 25 ± 3 msec (program 2).

Results

Atrioventricular Conduction Effects

Administration of up to 10 mg/kg dantrolene sodium intravenously caused no significant increase in A-V conduction parameters, with either paced or spontaneous rhythms. The HV interval actually declined slightly, but significantly, with 5 and 10 mg/kg of dantrolene. Dantrolene caused no significant change in spontaneous heart rate, and no systematic variation

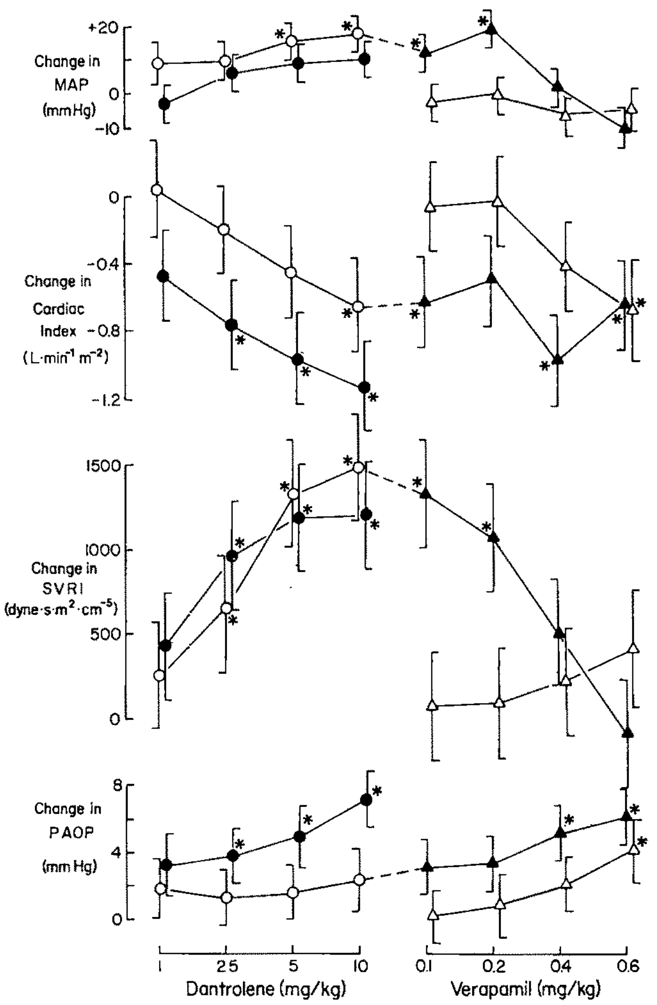

Figure 3. Changes in hemodynamic function with incremental doses of dantrolene and verapamil. Each point represents the average change from control in six animals at the indicated cumulative drug dosage. The error bar is the standard error of the average change from control. Values are plotted for the following: dantrolene alone, program 1 (○); dantrolene after prior verapamil administration, program 2 (●); verapamil alone, program 2 (△); verapamil after earlier dantrolene administration, program 1 (▲). * indicates an average change from control which is significant ($P < 0.05$) by analysis of covariance. Hemodynamic measurements were made while each animal was being paced at a constant rate. The paced heart rate in all animals averaged 175 ± 7 beats/min. The average (± SEM) control measurements were the following: mean arterial pressure, 141 ± 10 mm Hg (program 1) and 135 ± 3 mm Hg (program 2); cardiac index, 3.17 ± 0.23 (program 1) and 3.97 ± 0.40 $L \cdot min^{-1} \cdot m^{-2}$ (program 2); systemic vascular resistance index, 3571 ± 437 (program 1) and 2756 ± 277 $dyne\text{-}sec \cdot m^2 \cdot cm^{-5}$ (program 2); pulmonary artery occlusion pressure, 4.2 ± 0.6 mm Hg (program 1) and 5.8 ± 0.9 mm Hg (program 2). There was no significant difference in the average control values between protocols.

in conduction intervals was observed for the measurements made 10 min vs 20 min after dantrolene administration. In contrast, the PR and AH intervals increased significantly above the control level after 0.2 mg/kg and greater cumulative doses of verapamil.

The peak depressant effect of verapamil on A-V conduction did not coincide with the peak hemodynamic effect but occurred 10–25 min after drug administration. The increase in AH interval was observed both with paced and spontaneous heart rate, but there was no significant effect on HV interval. Figure 2 summarizes the changes in AH and HV intervals observed with spontaneous or paced rhythm during drug administration.

Treatment with 10 mg/kg dantrolene prior to verapamil administration appeared to enhance the effect of verapamil in lengthening the AH interval, but in no case was the effect significantly greater than that observed with verapamil alone. Prior treatment with dantrolene did cause the initial dose (0.1 mg/kg) of verapamil to significantly increase the paced AH interval above the control value. In the presence of dantrolene, the highest dose of verapamil significantly reduced spontaneous heart rate below control. When verapamil pretreatment preceded the dantrolene administration, dantrolene still had no additional effect on A-V conduction. In fact, all conduction intervals returned toward normal values during the course of dantrolene administration.

Although dantrolene created no marked enhancement of the effects of verapamil upon A-V conduction intervals, the final dose of verapamil (0.6 mg/kg cumulative) caused intermittent second degree heart block in four of six dogs when paced, and it caused intermittent complete heart block with junctional rhythm in one animal. Such disturbances were not observed with verapamil alone.

Hemodynamic Effects

Dantrolene (2.5–10 mg/kg) caused a significant rise in systemic vascular resistance index (SVRI), which was accompanied by an increase in mean arterial pressure (MAP) (5–10 mm Hg), as shown in Figure 3. A decrease in cardiac index (CI) occurred at a dose of 10 mg/kg, but there was no significant change in the PAOP or in pulmonary vascular resistance index (PVRI) with any dose of dantrolene alone. The changes in SVRI, MAP, and CI persisted in the presence of 0.1–0.2 mg/kg verapamil. Verapamil alone significantly depressed CI and increased PAOP with the final dose (total dose: 0.6 mg/kg).

In the presence of prior treatment with verapamil, smaller doses of dantrolene (≥ 2.5 mg/kg) significantly depressed CI below control, whereas PAOP was significantly increased. Similarly, when verapamil was administered after loading with dantrolene, a lower dose (0.4 mg/kg total) was found to depress CI and increase PAOP. The PVRI was also increased the control in the presence of both drugs. Due to the large standard deviation, the effect of any dose of drug, after prior treatment with the other drug (general linear model, employing Duncan's multiple range test), did not differ significantly from the effect of that same drug dose by itself.

The above results summarize the effects in six paced animals in each program. In the presence of spontaneous rhythm, greater variability in responses (nine animals in each program) was present. Dantrolene (5,10 mg/kg) did cause a rise in SVRI in both the presence and absence of verapamil. Only when the combination of dantrolene and verapamil were present together, however, were significant increases in PAOP and decreases in CI noted.

Serum Drug Levels and Skeletal Muscle Effects

The serum levels of dantrolene in six animals 25 min after the 1.0, 1.5, 2.5, and 5.0 mg/kg doses were 0.41 ± 0.05, 0.93 ± 0.12, 2.5 ± 0.3, and 7.6 ± 0.7 μg/ml, respectively, with prior verapamil treatment causing no apparent difference between groups. In three animals the dantrolene level declined to 3.2 ± 1.2 μg/ml after approximately 2.5 hr. Technical difficulties permitted verapamil concentrations to be determined in only two dogs in each program. In two animals, in the absence of dantrolene, the cumulative verapamil doses of 0.1, 0.2, 0.4, and 0.6 mg/kg gave serum levels of 17–22, 24–66, 49–92 and 65–95 ng/ml, respectively, when measured 20–25 min after the dosage. During the subsequent 2-hr administration of dantrolene, verapamil levels declined to 17–25 ng/ml. When verapamil was administered incrementally after dantrolene loading, the serum levels in two animals were approximately half those noted above, in which verapamil was given prior to dantrolene.

The incremental doses of dantrolene caused the twitch to be significantly depressed to 61 ± 2, 43 ± 3, 31 ± 3, and 23 ± 2% of control, in a dose-dependent manner. Administration of incremental doses of verapamil caused significant twitch depression (88 ± 5% of control) only after the final dose (0.6 mg/kg total). Verapamil did not, however, enhance the subsequent depression of twitch tension caused by dantrolene. Tension was depressed to 61 ± 4, 50 ± 6, 42 ± 6, and 38 ± 7% of control by the incremental dantrolene doses, after prior treatment with verapamil.

Discussion

Unlike verapamil, dantrolene causes no significant delay in A-V conduction under the conditions of these experiments. Possible dantrolene depression of A-V conduction was suggested by in vitro experiments in which it depressed calcium-dependent slow action potentials induced in the partially depolarized His-Purkinje system (8). Such calcium-dependent slow action potentials mediate conduction through the A-V node (11). In contrast, the calcium entry blocker verapamil increases the atrial His-bundle interval consistent with depressed A-V nodal conduction. Verapamil, particularly the (−) isomer, is known to block calcium-dependent slow action potentials. The (+) isomer of verapamil appears to block sodium channel-mediated fast action potential conduction at high concentrations (4 μM) (21). However, the highest serum level of verapamil documented in these experiments was only equivalent to 0.2 μM. Pacing at higher rates did tend to enhance the depressant effect of verapamil on A-V conduction, possibly due to the frequency-dependent blockade caused by this drug (21–23).

Verapamil caused a transient decrease in blood pressure that peaked within 2–6 min after drug dosage. In contrast, the maximum depressant effect of verapamil on A-V conduction occurred 10–25 min after administration of the drug, although serum concentrations should have declined substantially at this time. Other workers described similar effects in dogs, in which both serum and myocardial verapamil concentrations dropped prior to the peak effect on A-V conduction, occurring between 10–40 min in five animals (24). In the present study, the effects of verapamil on A-V conduction appear to be similar or slightly less than those observed by others for similar serum concentrations (24). The effects of verapamil did not appear to be enhanced by prior treatment with dantrolene, although significant increase in the A-H interval above control was observed at a lower dose of verapamil (0.1 vs 0.2 mg/kg dose). However, disruption of A-V conduction (second degree A-V block, junctional rhythm) was observed only when verapamil treatment followed earlier dantrolene loading, suggesting a potential interaction that did not approach quantitative significance with regard to measured parameters. When dantrolene was administered after verapamil treatment, the return toward normal AH conduction probably reflects gradual clearance of verapamil from serum, as observed in two animals studied.

In vitro evidence suggests that dantrolene depresses myocardial contractility (8–10), but no such obvious effect was observed in these studies. Dantrolene (≥ 2.5 mg/ml) did appear to increase systemic vascular resistance with depression of CI at the highest dose. Verapamil has been shown to depress myocardial contractility in a dose-dependent and frequency-dependent manner (21,22). Those effects were reflected in this experiment by a decreased CI and increased PAOP at the highest dose employed. Although vasodilation by verapamil is well described (16), a significant decrease in systemic vascular resistance was not observed. Hemodynamic changes and myocardial depression caused by verapamil may be counteracted by autonomic reflex changes and increased sympathetic tone (16). The light anesthetic technique employed (chloralose–urethane) may explain the absence of dramatic cardiovascular depression observed with verapamil. Previous studies combining volatile anesthetics with verapamil have demonstrated significant depression of cardiac performance (25,26).

The combination of verapamil and dantrolene caused significant depression of cardiac index from control and increases of PAOP that were not observed with either drug alone. Because direct statistical comparison demonstrated no enhancement of effects caused by pretreatment for any dose of either drug, the degree of interaction is probably not profound. It is noteworthy that during dantrolene administration after prior treatment with verapamil, the AH interval returned toward control, but CI continued to decline while PAOP increased. These effects may be due in part to the observed increase in systemic vascular resistance. However, when verapamil (0.4 mg/kg) was given after dantrolene, a significant decrease in CI and an increase in PAOP occurred even though SVRI was not different from control. Such effects are consistent with myocardial depression. Verapamil did tend to counteract the increase in systemic vascular resistance observed with dantrolene.

The changes caused by dantrolene, verapamil, or both, in cardiovascular performance in dogs observed in the present study were similar in many respects to those previously observed in pigs by Saltzman et al. (27). They also found that dantrolene alone (10 mg/kg total dose) caused a significant increase in mean arterial pressure, but no significant decrease in cardiac output, as observed here in dogs. More noteworthy was the significant decline in cardiac output observed after dantrolene administration in the presence of a continuous verapamil infusion. Complete A-V block occurred in all animals, and cardiac arrest in 80%. Furthermore, Saltzman et al. (27) also observed a significant increase in serum potassium with this combination of drugs. Although we did not specifically measure serum potassium, no change in the electrocardiogram suggesting elevated potassium (increased QRS duration, increased T-wave amplitude) was observed. The serum levels of dantrolene in the study in pigs were similar to the levels in dogs in the present study. The verapamil levels, however, were somewhat higher in the study in pigs, as a continuous infusion was employed. Although a different dosing regimen was employed in these two studies, it appears that myocardial contractility is similarly depressed in both species by the combined dantrolene–verapamil administration.

The study in pigs employed strains not known to be susceptible to malignant hyperpyrexia (MH), although in the present study there was no evidence of a hyperthermic response in any dogs employed (28). Although the myocardium of MH-susceptible strains or individuals may differ from the nonsusceptible, the question remains whether myocardial performance in susceptible animals might be affected differently by these drugs.

Dantrolene caused a clear dose-dependent decline in skeletal muscle twitch tension. After the final loading dose of dantrolene, addition of verapamil caused no further decline in twitch tension. During the 2-hr period of subsequent verapamil administration, serum levels of dantrolene declined to approximately one-half the level observed after the final loading dose, and twitch tension remained depressed. Verapamil by itself caused no marked reduction in twitch and did not appear to enhance the clear dose-dependent depression caused by dantrolene. Although verapamil appears to depress neuromuscular transmission in high doses (29), its role in skeletal muscle excitation–contraction coupling is less clear. External calcium is much less crucial in maintaining skeletal muscle twitch than in maintaining myocardial contractility. Consequently, blockade of calcium entry is less crucial (30). The effects of verapamil on skeletal muscle excitation–contraction coupling are unclear (31–33), and the effects at clinically relevant drug levels (< 50 ng/ml or 0.1 μM) remain to be demonstrated.

Dantrolene and verapamil do not appear to markedly interact in depressing A-V conduction, although verapamil treatment after dantrolene loading did frequently result in intermittant second degree heart block. However, these drugs in combination do appear to cause significant depression of myocardial performance. Although depression of skeletal muscle tension development by dantrolene is clearly demonstrated, verapamil administration had no additional effect. Therefore, in view of the potential for cardiovascular depression and dysrhythmias, with little evidence for enhanced therapeutic effect on skeletal muscle, the addition of verapamil to dantrolene therapy for malignant hyperpyrexia remains suspect.

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ANESTH ANALG
1986;65:259–66

A Comparison of Morphine, Fentanyl, and Sufentanil Anesthesia for Cardiac Surgery:

Induction, Emergence, and Extubation

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SANFORD TJ Jr, SMITH NT, DEC-SILVER H, HARRISON WK. A comparison of morphine, fentanyl, and sufentanil anesthesia for cardiac surgery: induction, emergence, and extubation. Anesth Analg 1986;65:259–66.

We compared anesthetic doses of three popular opiates, morphine (n = 10), fentanyl (n = 9), and sufentanil (n = 9) in patients undergoing cardiac surgery. Opiate administration after induction was based upon EEG and cardiovascular signs of the depth of anesthesia. Total doses were morphine, 4.4 ± 0.71 mg/kg, fentanyl, 95.4 ± 9.9 μg/kg, and sufentanil, 18.9 ± 2.2 μg/kg. Comparisons among opiates included times for induction of anesthesia, return of consciousness, return of spontaneous ventilation, return of adequate cardiovascular status, and extubation. The following times (mean and SEM*) were significantly ($P < 0.05$) shorter for sufentanil than for fentanyl or morphine: induction (15 ± 2.3 min, 5.9 ± 0.7 min, and 3.0 ± 0.2 min for morphine, fentanyl, and sufentanil, respectively); return of consciousness (morphine 109.7 ± 34.4 min, fentanyl 62.3 ± 17.9 min, sufentanil 17 ± 8.7 min); return of acceptable and stable cardiovascular status (morphine 587.3 ± 139.3 min, fentanyl 537.9 ± 144.8 min, sufentanil 173.7 ± 56.8 min); and extubation (morphine 1121.3 ± 61.8 min, fentanyl 1005.7 ± 77.7 min, sufentanil 533.3 ± 67.8 min). We conclude that sufentanil administered in the dosage range of 19 μg/kg allows more rapid induction, earlier emergence from anesthesia, and faster extubation of patients than either morphine or fentanyl.*

Key Words: ANALGESICS—morphine, fentanyl, sufentanil. ANESTHETICS; INTRAVENOUS—narcotic. ANESTHESIA—cardiovascular.

High-dose narcotic–oxygen anesthesia for cardiac surgery is popular not only for patients with poor left ventricular function but also for patients with good ventricular function undergoing surgery for coronary artery bypass graft. The commonly used narcotics for this high-dose technique have been morphine and fentanyl, although no direct randomized study comparing the two has been published. Recently the narcotic agonist sufentanil has been introduced into this country. This study assessed anesthesia with morphine, fentanyl, and sufentanil in high doses with oxygen, and compared them in terms of nine important time intervals before, during, and after anesthesia for cardiac surgery. We observed that sufentanil was associated with significantly shorter times in seven of the nine intervals studied.

Methods

The protocol was approved by both the University and Veterans Administration Hospital Human Research Committees. Informed written consent was obtained from each patient.

Thirty patients undergoing cardiac surgery, 27 coronary artery bypass grafts, and three aortic valve replacements, were randomly assigned morphine–oxygen, fentanyl–oxygen, or sufentanil–oxygen anesthesia. Patients ranged in age from 39 to 66 years. Each patient received preanesthetic medication with morphine, 0.13 ± 0.3 mg/kg, and scopolamine, 4.9 ± 1.5 μg/kg intramuscularly, 1 hr before scheduled induction of anesthesia.

All patients had the following placed before induction of anesthesia: ECG (lead CMV$_5$), EEG (Fp$_1$–O$_1$,Fp$_2$-O$_2$), blood pressure cuff, radial arterial

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catheter (20-g Teflon), and a thermodilution Swan–Ganz catheter via the right internal jugular vein. All data were recorded on a Vetter tape recorder and a Hewlett–Packard 8-channel strip chart recorder. The EEG was recorded and displayed on a computer-processed EEG, the Neurometrics (1). Cardiac output was continuously monitored with a beat-to-beat pulse–contour cardiac output computer. The cardiac output computer was calibrated with triplicate thermodilution cardiac outputs for each patient. Before induction, cardiovascular variables, including thermodilution cardiac output, mean arterial pressure, mean pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure, and heart rate were obtained.

The choice of narcotic was randomized. We diluted the morphine (3 mg/ml) and sufentanil (10 μg/ml) so that each would be approximately equivalent to fentanyl (50 μg/ml). We administered oxygen to all patients via the anesthetic circuit before induction. All patients were given pancuronium, 25 μg/kg, before the start of induction to attenuate chest wall rigidity. Induction of anesthesia was begun slowly with 1 ml of the chosen narcotic given as a bolus each of the first 4 min; 2 ml each of the next 3 min; and 5 or 10 ml each min for the duration of the surgery, depending upon EEG and cardiovascular signs of inadequate anesthesia. After induction supplemental opiate was given until the EEG showed signs of adequate anesthesia and the cardiovascular variables were stable. No other anesthetic or sedative agents were used except pancuronium (0.02–0.08 mg/kg), or metocurine (0.1–0.2 mg/kg), or both, for relaxation administered after the loss of consciousness.

We measured the following times: 1) Duration of anesthesia (the time from the start of induction to the end of surgery). 2) Time to loss of consciousness (the time between the beginning of opiate administration and the time at which the patient would not respond to the verbal command, "(Patient's name), open your eyes!" repeated loudly three times; we defined this as "induction time."

The following times were measured from the end of anesthesia, defined as the time the patient was transferred to the transport bed: 3) Return of consciousness, divided into three levels—level I, return of spontaneous movement; level II, the return of response to voice (arousal); level III, the return of appropriate response to a verbal command. 4) Return of spontaneous ventilation, defined as a tidal volume > 50 ml, as measured by a Wright respirometer, with a rate > 6.5) Return of acceptable arterial blood gas tensions during intermittent mandatory ventilation, i.e., $P_{O_2} \geq 80$ torr, $P_{CO_2} \leq 45$ torr, and pH ≥ 7.35 at an $F_{IO_2} < 0.6$. 6) Return of the ability to perform certain mechanical ventilatory tasks during intermittent mandatory ventilation (IMV), as defined by a tidal volume ≥ 7 ml/kg, a mean inspiratory pressure ≤ -20 cm H_2O, vital capacity ≥ 10 ml/kg. 7) Acceptable and stable cardiovascular status, defined as three consecutive measurements at 15-min intervals of a systolic arterial pressure within 10% of preoperative value, pulmonary capillary wedge pressure (PCWP) ≤ 20 mm, the absence of need for vasopressors or vasodilators, the absence of dysrhythmias, and the absence of abnormal bleeding from the chest tubes. 8) Extubation, performed when patients satisfied the criteria in items 5, 6, and 7, after 1 hr of unassisted spontaneous ventilation. All postoperative measurements were made by the same pair of observers, who were unaware of which opiate had been administered.

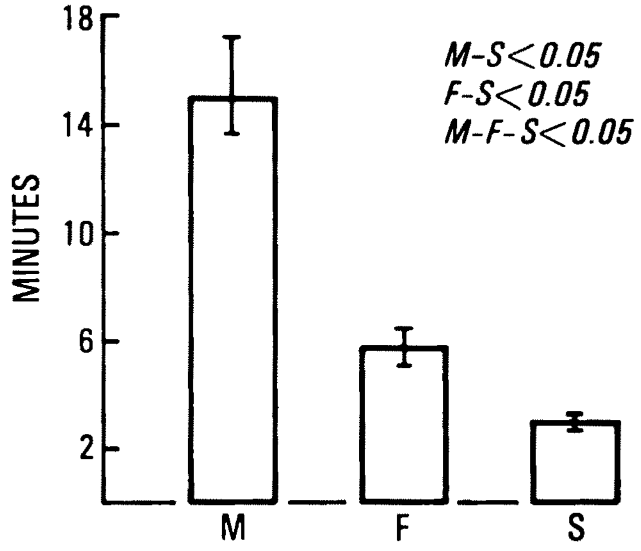

Figure 1. The time between the beginning of narcotic administration and the inability of the patient to respond to a verbal command was defined as the induction time. Sufentanil resulted in a significantly more rapid induction of anesthesia than did either morphine or fentanyl.

If a patient satisfied all the respiratory criteria for extubation, but extubation was delayed because of cardiovascular complications, such as excess bleeding that might have led to a return to the operating room, we used the time at which the patient satisfied the blood gas and ventilatory criteria during one consecutive hour of unassisted spontaneous ventilation as the time to extubation. Two patients given sufentanil, and one patient each receiving morphine or fentanyl, fell into this category. Two patients were omitted from the study, one who died immediately after the operation (fentanyl) from a hypokalemic dysrythmia, and one who needed an intraaortic balloon pump immediately after the operation (sufentanil). No sup-

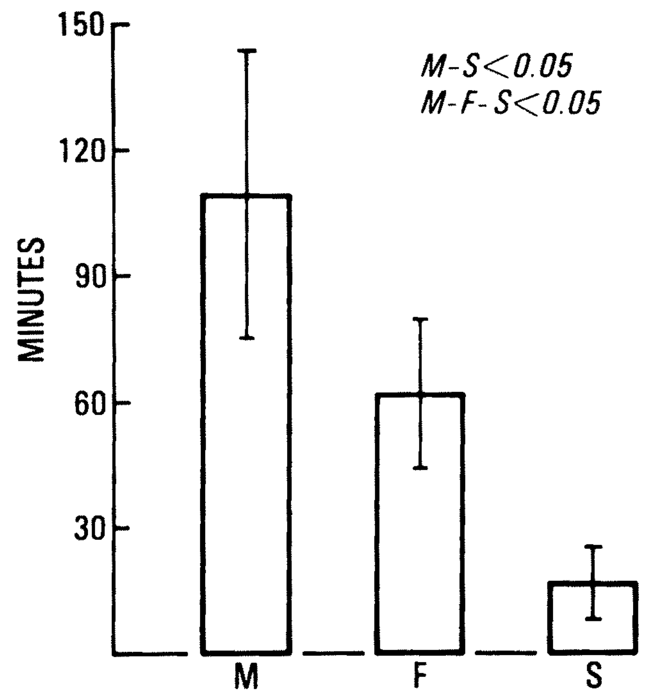

Figure 2. The times to the return of spontaneous movement after the end of surgery. The sufentanil group was associated with significantly more rapid return of spontaneous movement than either the morphine or fentanyl groups.

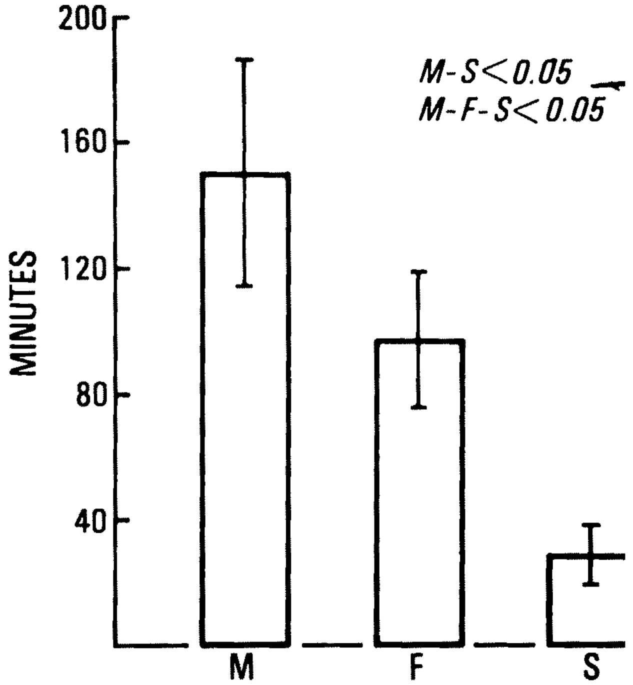

Figure 3. The time between the end of surgery and the time which the patient could respond to a verbal stimulus was signi cantly shorter after sufentanil than after either morphine or fentany

plemental opiates or sedative medications were administered in the intensive care unit prior to extubation.

The null hypothesis that the average time intervals for each drug did not differ significantly was tested by one-way analysis of variance (ANOVA). For those time intervals that demonstrated significance with the ANOVA, we then made multiple comparisons among drugs, by using the Student–Newman–Keuls procedure. The null hypothesis was rejected if $P < 0.05$.

Results

Total Drug

All values in this paper are given as mean ± SEM. The total amount of each narcotic administered was morphine, 4.4 ± 0.71 mg/kg, fentanyl, 95.4 ± 9.9 μg/kg, and sufentanil, 18.9 ± 2.2 μg/kg.

Duration of Anesthesia

There was no statistically significant difference in the total times of anesthesia and duration of surgery in the three groups (morphine, 341 ± 18 min, fentanyl, 318 ± 33.8 min, sufentanil, 356.7 ± 26 min). The anesthetic–surgical times for the three patients undergoing aortic valve replacements were 310, 312, and 367 min; all these patients received sufentanil. In addition, the times from the end of bypass to arriv in the intensive care unit were not statistically diffe ent (morphine, 103 ± 11.1 min, fentanyl, 94 ± 13. min, sufentanil, 119 ± 12.6 min).

Induction Times

Figure 1 shows that induction times with sufentan (3.0 ± 0.2 min) or fentanyl (5.9 ± 0.7 min) wer significantly shorter than with morphine (15 ± 2. min). The time for induction of anesthesia with su fentanil was significantly more rapid than with fentanyl

Return to Consciousness

Level I—(Fig. 2). The time to return of spontaneou movement was significantly faster after administra tion of sufentanil (17.3 ± 8.7 min) than after eithe morphine (109 ± 34.4 min) or fentanyl (62.3 ± 17. min). The difference between morphine and fentan was not statistically significant.

Level II—(Fig. 3). The time for the return of r sponse to voice was significantly shorter with sufer tanil (28.4 ± 9.8 min) than with either fentan (97.0 ± 21.6 min) or morphine (150.0 ± 36.2). Th time interval was also shorter with fentanyl than wit morphine, but not significantly.

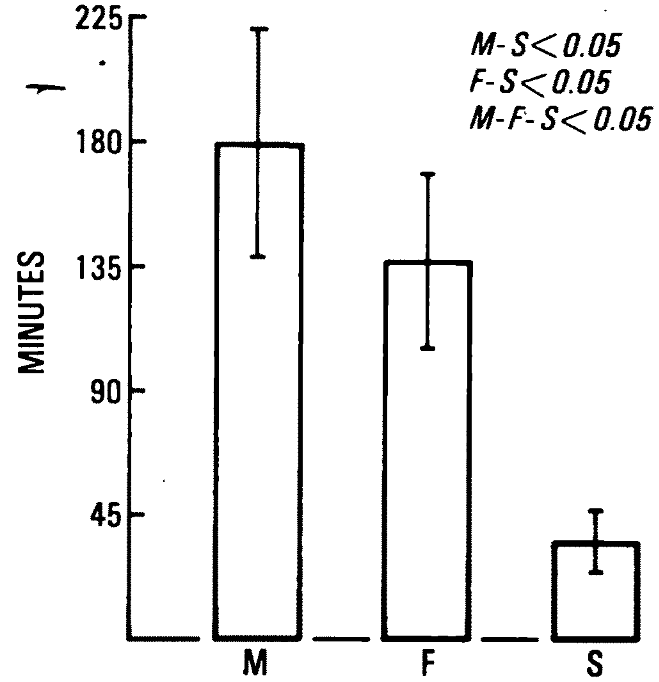

Figure 4. The interval between the end of surgery and the time at which patients could respond with purposeful movement to a verbal command was significantly more rapid after sufentanil than after either morphine or fentanyl.

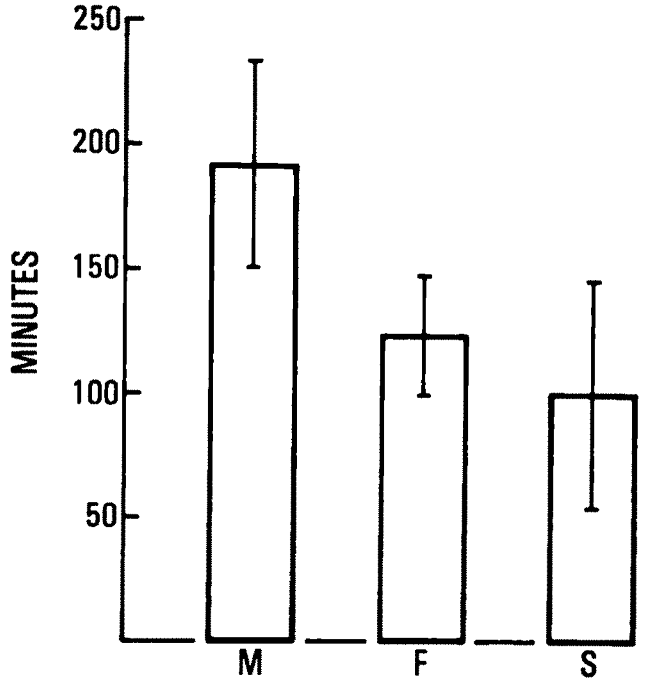

Figure 5. The time for the return of spontaneous ventilation was not significantly different for any of the three groups.

Level III—(Fig. 4). The time for the return of appropriate response to a voice command was significantly shorter after administration of sufentanil (35.7 ± 11.7 min) than after either morphine (180.0 ± 41.3 min) or fentanyl (137.9 ± 31.9 min). This time interval was also shorter with fentanyl than with morphine, but again not enough to be statistically significant.

Return of Spontaneous Ventilation

There were no statistically significant differences among the three drugs, although spontaneous ventilation tended to return more rapidly after sufentanil (100.9 ± 46.6 min) than after morphine (192.3 ± 41.5 min) or fentanyl (124.0 ± 24.3 min) (Fig. 5).

Return of Acceptable Arterial Blood Gas Tensions

There were no statistically significant differences among the three drugs (Fig. 6).

Return of Adequate Ventilation

The time required before patients were able to adequately perform mechanical ventilatory maneuvers was significantly less after sufentanil (336.0 ± 63.2 min) than after morphine (785.4 ± 110.9 min) or fentanyl (583.8 ± 64.8 min). There was no significant difference between fentanyl and morphine (Fig. 7).

Return of Acceptable and Stable Cardiovascular Status

There were wide differences in times among morphine (587.3 ± 417.5 min), fentanyl (537.9 ± 434.6 min), and sufentanil (173.7 ± 170.5 min). The differences were statistically significant between sufentanil and both fentanyl and morphine. There was no difference between fentanyl and morphine (Fig. 8).

Extubation

The time until extubation could be accomplished was significantly shorter with sufentanil (533.3 ± 67.8 min) than with either morphine (1121.3 ± 61.8 min) or fentanyl (1005.7 ± 77.7 min). There was no statistically significant difference between fentanyl and morphine (Fig. 9).

Discussion

We observed that high-dose sufentanil produced both a more rapid induction of anesthesia and a more rapid emergence from anesthesia than either fentanyl or

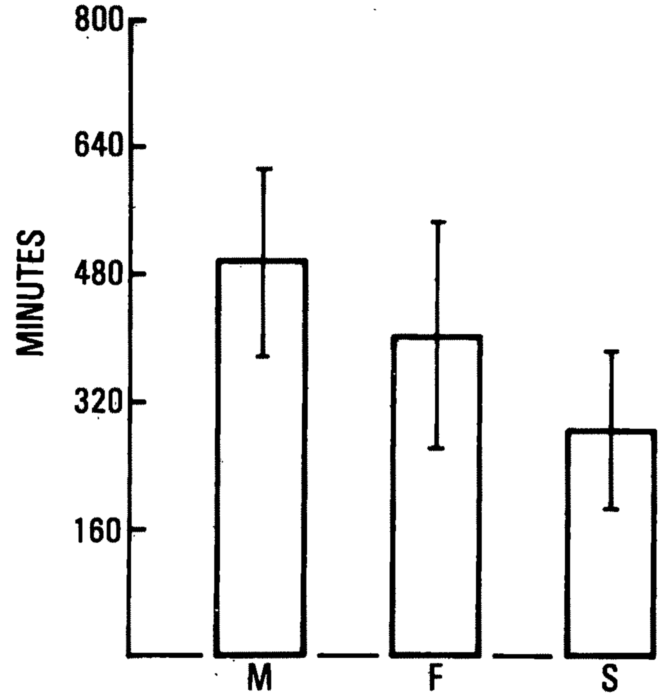

Figure 6. The times for the return of acceptable arterial blood gases while the patient was being mechanically ventilated were not significantly different among the three groups.

morphine. We were able to detect the difference among agents because of the relatively slow method of injection. The more rapid onset of sufentanil, in these circumstances, aids the anesthetist who wishes to titrate an opiate. The difference between fentanyl and sufentanil disappears when the agents are given in large doses and injected rapidly (10).

Although the speed of induction of anesthesia for cardiac surgery is important, the importance of a rapid emergence as well as an early extubation has not been well documented. There is a growing trend not only among cardiovascular surgeons but also among anesthesiologists to extubate their patients early. At some institutions patients are extubated before leaving the operating room, provided they satisfy guidelines related to the degree of difficulty of the surgery and to cardiovascular stability immediately after bypass (Blackstone, E.H., personal communication). Quasha et al. showed that cardiac patients who had been anesthetized with halothane and oxygen, and who were extubated early, suffered less cardiopulmonary morbidity and needed less sedative and pain medication than patients who remained intubated overnight (2). In addition, Foster et al. reported that early extubation after coronary artery bypass graft surgery was associated with no mortality and with lower surgical intensive care unit costs (3).

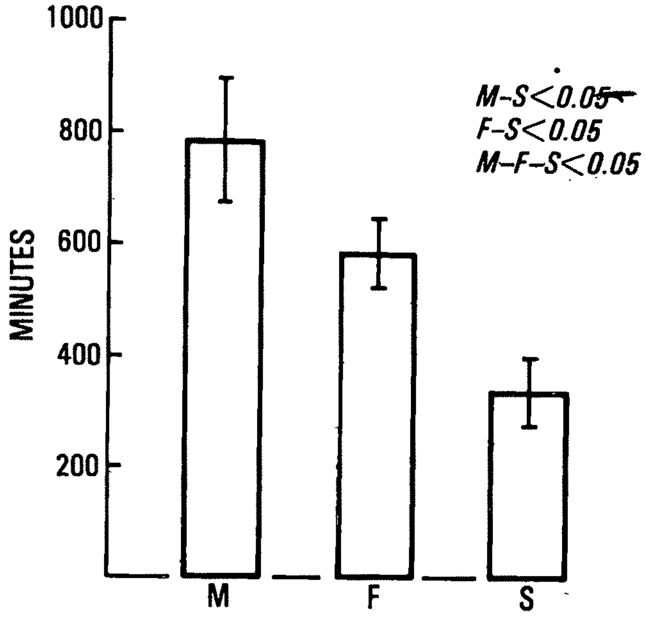

Figure 7. The time before patients were able to satisfactorily perform mechanical maneuvers was significantly faster after sufentanil than after either morphine or fentanyl.

Because there do not seem to be strict criteria for extubation after cardiac surgery in the literature (4), we chose multiple criteria from both the respiratory and the cardiovascular systems to assure maximum patient safety. Among these criteria, the vital capacity measurement was useful in at least two ways. It not only helps measure ventilatory mechanics, but it also requires that the patient be awake and able to follow a rather complex command. Results with the vital capacity measurement after anesthesia with sufentanil suggest a sustained alertness and attentiveness that appeared earlier with this agent, results supported by our clinical observations of these patients. In contrast, comparable sustained alertness appeared later with fentanyl, and not at all on the day of surgery with morphine. Patients given high-dose morphine anesthesia were unable to satisfy the criteria for extubation on the day of operation, and patients receiving fentanyl were only slightly better. Only those patients receiving sufentanil experienced a relatively early extubation.

Our criteria for extubation were satisfactory in patients having cardiac surgery. None of the patients required reintubation, including those undergoing early extubation after administration of sufentanil. There was no cardiopulmonary morbidity among any of the three groups that we could attribute to intubation or extubation.

Although we did not reverse muscle relaxants at the end of the case, all patients received statistically

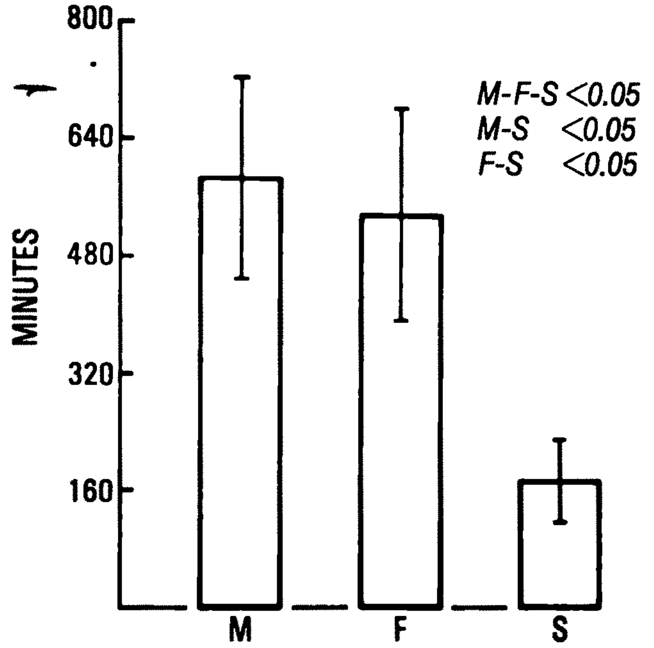

Figure 8. The time for return of acceptable and stable cardiovascular status was significantly faster with sufentanil when compared with morphine or fentanyl. There was no difference between fentanyl and morphine.

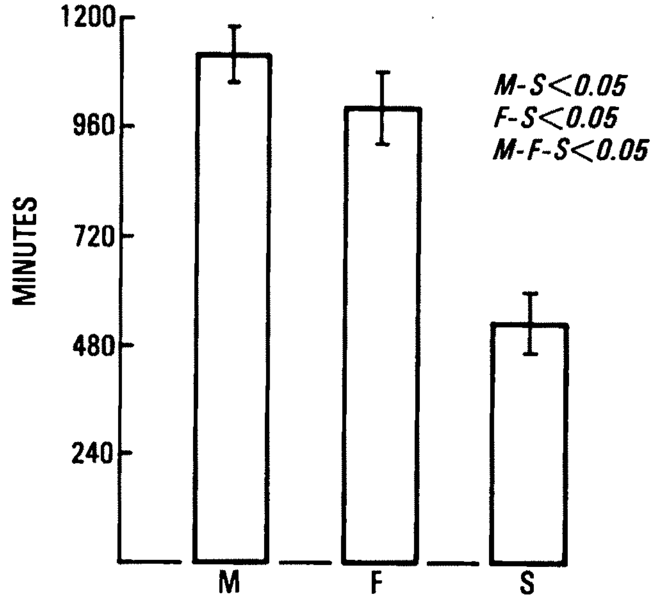

Figure 9. Patients receiving sufentanil satisfied the cardiovascular and respiratory criteria significantly faster than patients who received either morphine or fentanyl and were therefore able to be extubated earlier.

similar amounts of the metocurine–pancuronium combination. Also the fact that there were no statistically significant differences in the times for return of spontaneous ventilation and return of adequate arterial blood gas tensions suggests that the muscle relaxants did not affect the relative times of extubation after the three agents.

Howie et al. (5,6) in two recent reports found no difference between fentanyl, 125 μg/kg, and two different doses of sufentanil, 20 and 25 μg/kg, in terms of postoperative time intervals. In the group receiving sufentanil, 25 μg/kg, Howie et al. (5) found that the times from the beginning of anesthesia to return of response to voice (sufentanil, 721 min), return of spontaneous ventilation (sufentanil, 991 min), and time to extubation (sufentanil, 1394 min) were not significantly shorter when compared to fentanyl—results that differ from those of the present study (Fig. 10). In the group receiving 20 μg/kg of sufentanil, Howie et al. (6) also reported that there were no significant differences in postoperative time intervals measured from the end of surgery to the time of emergence and to the time of extubation when patients receiving high-dose fentanyl were compared with those receiving sufentanil.

Because the duration of anesthesia was not significantly different among our three groups, we conclude that the total time of anesthesia did not influence our postoperative time intervals. It is not possible to determine whether the duration of anesthesia affected the postoperative time intervals in either of the studies by Howie et al.

Although the criteria for emergence time in Howie's studies are not exactly comparable to ours, we feel that the differences in emergence time is due to the method of sufentanil and fentanyl administration. In both of the studies by Howie et al. supplemental sufentanil was administered on an empiric basis. In contrast we administered supplemental dosage based on continuously displayed and recorded cardiovascular variables and interpretation of the processed EEG (1). Although not proven in this study, it would seem advantageous to administer these agents on an individualized basis, titrating according to individual responses, in order to achieve relatively rapid emergence and early extubation.

In addition, in this study it was necessary to break some long standing habits, particularly that of delaying extubation until the morning after surgery. In our intensive care unit, injections of morphine had been customarily given to achieve this goal. If the effort to extubate early is not made, it may be difficult to establish a difference between the times to extubation for any two agents.

A previous report (1) demonstrated that in these patients the quantitative EEG responses to fentanyl and sufentanil were similar, suggesting that the depth of anesthesia was equivalent with these two agents.

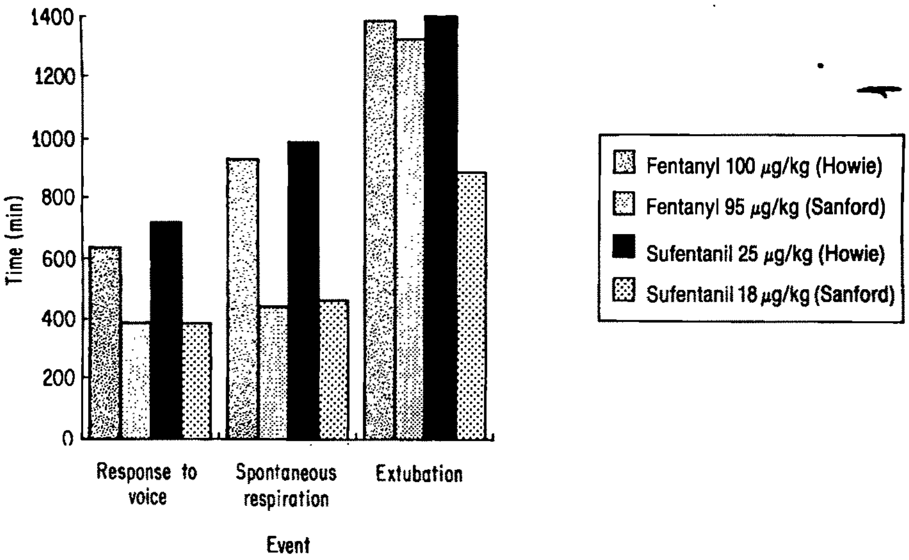

Figure 10. Comparison of the times of several postoperative events between patients receiving sufentanil, 18.9 ± 2.2 μg/kg or 25 μg/kg (5), shows that smaller doses were associated with significantly shorter times required to reach the postoperative milestones. All time intervals were measured from induction of anesthesia, in contrast to Figures 2–9 where intervals were measured from the end of surgery.

In addition, the quantified cardiovascular stability of these patients was similar with the two agents, with a less extensive use of the vasoactive agent with sufentanil (Smith N.T. et al., unpublished results). This previous report, combined with the present study, indicates that patients wake up more rapidly after sufentanil than after equivalent levels of anesthesia produced by fentanyl. This study also indicates that the price of cardiovascular stability, in terms of prolonged postoperative recovery, is less with sufentanil than with fentanyl.

In contrast to the patients receiving fentanyl or sufentanil, the EEG of those patients receiving morphine indicated a lighter depth of anesthesia (1), whereas cardiovascular instability was marked (Smith N. T. et al., unpublished results). In spite of these two indications of lighter anesthesia, the postoperative recovery from morphine was agonizingly slow. Neither of the two alternatives with morphine seem attractive: increase the dose for greater cardiovascular stability at the probable cost of an even more prolonged awakening, or reduce the dose to achieve a more rapid awakening at the probable cost of even greater cardiovascular instability. In our experience, morphine is not the anesthetic agent of choice.

In general, in patients receiving very large doses, induction of and recovery from anesthesia seem to be more rapid with sufentanil than with either fentanyl or morphine. A more rapid induction is related to the speed of crossing the blood–brain barrier. Drugs that are more lipid-soluble and less ionized at body pH tend to enter the central nervous system more rapidly; sufentanil satisfies both of these requirements. Offsetting these factors may be the greater degree of protein binding of sufentanil than that of fentanyl. This may mean that there is less free sufentanil available for entering the central nervous system than fentanyl (8). Our data would indicate that in our study the former factors predominate.

Another possible factor contributing to the more rapid induction with sufentanil would be the ratio of sufentanil to fentanyl doses in our study. At 1:5, the ratio was on the high end of the accepted potency ratios of 1:5–10. In general, a higher dose of an agent would lead to a more rapid induction of anesthesia (Moldenhauer CC, personal communication). However, based on EEG estimates, the doses are believed to be equivalent (1).

One of the potential explanations for the more rapid recovery with sufentanil may be related to the pharmacokinetics of these agents. In particular, the terminal elimination half-life in humans of sufentanil (5 μg/kg) is 2.7 hr (7), less than the reported terminal elimination half-lives of fentanyl (6.4 μg/kg) or morphine (1 mg/kg), namely 3.7 hr (8) and 4.5 hr (9), respectively. The shorter half-life of sufentanil is probably related to its apparent smaller volume of distribution (7). Note, however, that the relative dose of sufentanil in the above comparison study is much larger than that of fentanyl (1:1.3, rather than 1:5–1:10), suggesting that the differences in terminal half-lives may be greater than is commonly assumed. Thus a more rapid return of consciousness and ventilatory mechanics may be based on the faster elimination of sufentanil when administered in high doses as compared to that of either fentanyl or morphine.

One of the puzzling results in our study was the more rapid return of cardiovascular stability in patients given sufentanil (Fig. 8). A potential explanation of this phenomenon may be based on the rapid

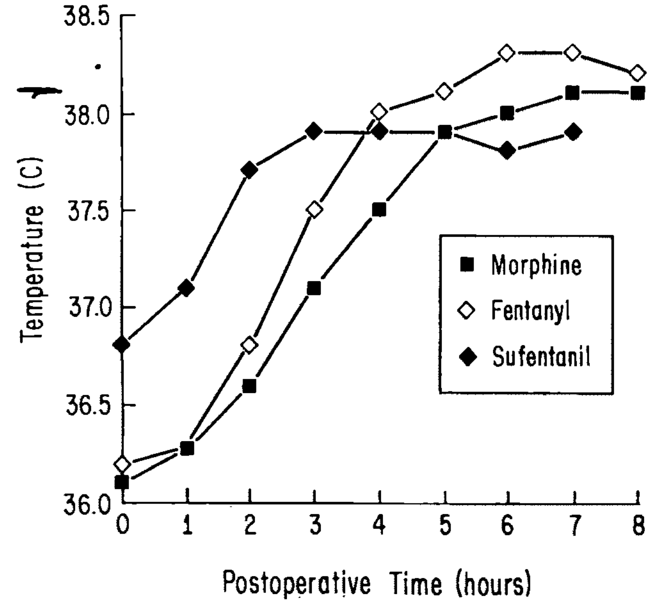

Figure 11. Rectal temperature as a function of time. Patients given sufentanil appeared to reach a normal postbypass temperature more rapidly than patients given either morphine or fentanyl, although the differences at any postoperative time were not statistically significant.

return of normal body temperature after bypass. We examined rectal temperature after bypass but could find no statistically significant differences, although patients receiving sufentanil seemed to attain stable postoperative temperatures sooner (Fig. 11). Because there was no statistically significant difference in the times between the end of bypass and the end of surgery for any of the three opiates, we eliminated this as a factor influencing this time interval.

In summary, our study showed that morphine produced prolonged induction of anesthesia and prolonged emergence. Patients receiving high-dose fentanyl also experienced a relatively prolonged emergence. However, although the difference between the mean time intervals for morphine and fentanyl were often large, a statistically significant difference was seen only for induction time. By using our criteria for extubation, there was no significant difference between fentanyl and morphine. On the other hand, patients given sufentanil had more rapid inductions of anesthesia and earlier extubations after surgery. Because sufentanil produces cardiovascular stability similar to that associated with fentanyl, but with less need for inotropic or vasoactive agents (Smith N. T. et al., unpublished results), and with an earlier awakening and extubation, sufentanil appears preferable to fentanyl as an anesthetic in cardiac surgery.

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Hypoxemia after General Anesthesia in Children

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MOTOYAMA EK, GLAZENER CH. Hypoxemia after general anesthesia in children. Anesth Analg 1986;65:267–72.

Postoperative hypoxemia has been well documented in adults but not in infants and children, although they are potentially more susceptible to airway closure and to disturbances in pulmonary gas exchange. In a prospective study, we measured arterial oxygen saturation (SaO_2) with a pulse oximeter in 97 ASA class I infants and children breathing room air before and after general anesthesia for superficial surgical procedures. Mean preoperative SaO_2 was 97.6 ± 0.15% (SEM). On arrival in the recovery room after anesthesia mean SaO_2 in room air had decreased significantly ($P < 0.01$) to 93.0 ± 0.49% (range 100–71%), corresponding to calculated arterial oxygen tension (PaO_2) of about 66 mm Hg. The second reading, 5–15 min later, also showed a statistically significant ($P < 0.01$) decrease in SaO_2 (94.1 ± 0.35%). There was no statistical difference in SaO_2 between patients who received inhalation anesthesia alone and those who were given narcotics. There was also no correlation between postoperative reduction in SaO_2 and duration of anesthesia or patient age. Of 67 patients who were asleep on arrival in the recovery room, 47 who remained asleep at the second SaO_2 reading had an average increase in SaO_2 of less than 1%. In contrast, in those patients who awoke, average SaO_2 increased more than 4% during a similar time period—a difference that was statistically significant ($P < 0.02$).

Key Words: ANESTHESIA—pediatric. HYPOXIA—postanesthetic. MONITORING—oxygen saturation.

In adults general anesthesia is associated with reduction of the resting lung volume, or functional residual capacity (FRC) (1,2), and an increase in the alveolar–arterial oxygen tension gradient $P(A–a)O_2$ (3–5). Because elastic recoil of the thorax and lungs is low in children, particularly in those less than 1 yr of age, the reduction in FRC may be exaggerated (6). Thus, in children, airway closure and associated ventilation/pulmonary perfusion ($\dot{V}/\dot{Q}$) imbalance and intrapulmonary shunting are likely to occur during general anesthesia and continue into the postoperative period. If children are allowed to breathe room air, oxygen desaturation of hemoglobin may result. Postoperative hypoxemia has been studied in adults (4,7), but not in infants and children. Recently, pulse oximetry has become clinically available, providing a means of continuously and noninvasively measuring arterial oxygen saturation (SaO_2) (8). The purpose of this study was to investigate the incidence, degree, and duration of postanesthetic hypoxemia in otherwise healthy infants and children, who were not given supplemental oxygen in the postanesthetic recovery room.

Methods

Included in the study were 97 ASA physical status I infants and children (mean age, 4.2 yr; range, 1 month to 17 yr) scheduled for relatively simple elective surgical procedures, such as myringotomy, inguinal herniorrhaphy, and orthopedic procedures on the lower extremities, under general anesthesia. We excluded patients scheduled for thoracic or abdominal surgery and those clinically judged to require supplemental oxygen postoperatively. The study was approved by the institutional review board for experimentation involving human subjects.

Sixty-two patients did not receive premedication and were anesthetized with halothane or isoflurane with nitrous oxide. The remaining 35 received narcotics either as premedication or as a supplement to general anesthesia; narcotics were not reversed during or after anesthesia. Thirty-three patients had oral endotracheal intubation, usually after administration of intravenous atropine (0.02 mg/kg) and succinylcholine (1.0 mg/kg), and 64 breathed by mask. A modified Mapleson D partial rebreathing system (coaxial

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circuit) was used for all patients, with or without assisted or controlled ventilation. Patients who were given nondepolarizing muscle relaxants ($n = 16$) received intravenous doses of atropine (0.03 mg/kg) and neostigmine (0.07 mg/kg) for reversal. All patients breathed 100% oxygen for at least 3 min after nitrous oxide was turned off and adequate spontaneous breathing well established. Children anesthetized through an endotracheal tube were given oxygen by mask for several additional minutes after extubation. The patients were then transferred in the lateral position to the postanesthetic recovery room while breathing room air.

Values of Sao$_2$ were measured by attaching the self-adhesive sensor of a pulse oximeter (Nellcor, Inc., Hayward CA) to a finger or toe and directly reading a digital display. Preoperative measurements were made in the waiting area within 15 min before anesthesia. The patients were awake, either sitting or lying in the bed, and with a few exceptions were not crying. Postanesthetic measurements of Sao$_2$ were made shortly after arrival in the postanesthetic recovery room and again 5–15 min later (mean, 7.7 min). All patients were breathing room air spontaneously, without an artificial airway. Most patients were in the lateral position when Sao$_2$ was measured in the recovery room; some awake patients were in the supine position. The duration of room-air breathing from the last breath of 100% O$_2$ in the operating room to the first postoperative Sao$_2$ measurement in the recovery room, was 3–5 min. The average level of Sao$_2$ on a digital readout accompanied by an accurate, consistent display of arterial pulsation during a period of up to 3 min was recorded. If Sao$_2$ was less than 90%, supplemental oxygen was given by mask. The heart rate was recorded at the time of Sao$_2$ measurement. Arterial oxygen tension (Pao$_2$) was estimated from Sao$_2$, assuming that pH and Pco$_2$ were normal, and using a Severinghaus nomogram, which was derived from a standard oxygen dissociation curve of adult blood corrected for pH and Pco$_2$ (9). Adequacy of ventilation was assessed clinically by observing the expiratory air flow from the nose or mouth and the movement of the thorax, with or without auscultation with a stethoscope. The degree of airway obstruction was scored as absent, mild (light snoring with adequate ventilation), or moderate (necessitating a position change or a nasopharyngeal airway).

All data are expressed as mean ± SEM. For statistical analysis we used the least-squares method for regression analysis and analysis of variance of repeated measures followed by the appropriate *t*-test; when comparison of two sets of numbers was made, we used paired *t*-tests. A *P* value of <0.05 was considered statistically significant.

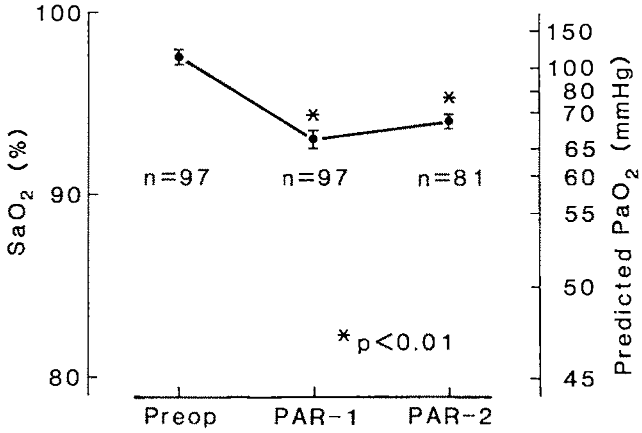

Figure 1. Mean (± SEM) oxygen saturation (Sao$_2$) measured with a pulse oximeter in children before anesthesia (preop), on arrival in the postanesthesia recovery room (PAR-1), and 5–15 min later (PAR-2). There is a statistically significant ($P < 0.01$) reduction in Sao$_2$ in PAR-1 and PAR-2 periods compared with preoperative values. Estimated Pao$_2$ is from Severinghaus (9).

Results

On arrival in the postanesthetic recovery room, all patients had clinically adequate ventilation. Six patients, all of whom had received narcotics, had mild upper airway obstruction (light snoring) without apparent disturbance in ventilation. None had moderate or severe airway obstruction or required an artificial airway.

The mean preoperative Sao$_2$ was 97.6 ± 0.15%. On arrival in the recovery room, the mean Sao$_2$ in room air had decreased significantly ($P < 0.01$) to 93.0 ± 0.49%, with a range of 100–70% (Fig. 1). Assuming a normal acid–base balance and hemoglobin–oxygen affinity, an Sao$_2$ of 93% corresponds to a Pao$_2$ of 66 mm Hg according to the Severinghaus nomogram (9); and an Sao$_2$ of 71% corresponds to a Pao$_2$ of 37 mm Hg. The second Sao$_2$ values, recorded in 81 patients, showed a slight but significant ($P <$ 0.01) increase (mean, 94.1 ± 0.35%) yet remained significantly ($P < 0.01$) below the mean preoperative value. In 48 children the Sao$_2$ was greater at the second than at the first reading, in 28 it decreased, and in 5 it remained the same. Of the 28 patients who had a higher first Sao$_2$ value, 7 had Sao$_2$ values at or above 99% (higher than preanesthetic values), probably indicating the residual effect of O$_2$ breathing. During this early postanesthetic period, 43 patients (43%) had a lowest Sao$_2$ at or below 91% (Pao$_2$ < 60 mm Hg).

Table 1. Comparison of Anesthetic Techniques in Relation to Postoperative SaO$_2$ (mean ± SEM) as Measured with Pulse Oximetry

Group	Period	n	SaO$_2$ (%)	Difference (cf preop)
Inhalation anesthesia alone (no premedication)	Preoperative	62	97.7 ± 2.0	
	PAR-1[a]	62	93.3 ± 0.61	$P < 0.01$
	PAR-2[b]	43	93.8 ± 0.48	$P < 0.01$
With narcotic (including premedication)	Preoperative	35	97.6 ± 0.24	
	PAR-1	35	92.6 ± 0.86	$P < 0.01$
	PAR-2	35	94.4 ± 0.51	$P < 0.01$

[a] PAR-1, on arrival in postanesthetic recovery room.
[b] PAR-2, 5–15 min later in postanesthetic recovery room.
There is no statistically significant difference between the two groups.

There was no statistically significant difference in heart rate between normoxemic and hypoxemic patients.

We compared the SaO$_2$ values in children who did and who did not receive narcotics, either as premedication or as part of general anesthesia (Table 1). In both groups the mean preanesthetic SaO$_2$ was 97.6%. In the 62 patients who did not receive narcotics, the mean SaO$_2$ was 93.3% at the first reading and 93.8% at the second reading. In the 35 children who received narcotics the mean first postanesthetic SaO$_2$ was 92.6%, and the mean second postanesthetic value increased to 94.4%, which was significantly ($P < 0.05$) higher than the first reading. There was, however, no significant difference in the extent of reduction in SaO$_2$ between the two groups at either the first or the second reading. The mean SaO$_2$ in the six children who had mild airway obstruction was lower (87.8 ± 3.5%; range, 95–71%) than the group mean, but the difference was not statistically significant.

There was no correlation between age and the degree of postoperative oxygen desaturation of hemoglobin; the two children who had marked hypoxemia, however, were 2 and 5 yr of age (Fig. 2). The mean duration of anesthesia was 53.4 min, with a range of 10–270 min. There was no significant correlation between SaO$_2$ and the duration of anesthesia.

Table 2 summarizes the relation between state of wakefulness and SaO$_2$. Of 68 children who were asleep when SaO$_2$ was initially measured in the postanesthetic recovery room (PAR-1), 47 were still asleep at the second reading (PAR-2); the remaining 21 patients awoke between the first and second measurements. In children who remained asleep, SaO$_2$ increased from the first reading by an average of less than 1%. In contrast, in those who awoke shortly after the first SaO$_2$ measurement in the recovery room, whether crying or calm, the second SaO$_2$ increased by an average of more than 4% from the first measurement in the recovery room. There was a statistically significant difference ($P < 0.02$) in the extent of increase in SaO$_2$ between the two groups.

Discussion

Pulmonary gas exchange deteriorates during general anesthesia (1,3,7). In adults the increase in P(A–a)O$_2$ continues into the early postoperative period, even after minor surgical procedures, and may result in hypoxemia if patients are allowed to breathe room air (7,10). Infants and children are more vulnerable to airway closure (6,11), and thus more likely to develop postoperative disturbances in pulmonary gas exchange. However, information on postoperative hypoxemia in pediatric patients is lacking, partly because there has not been a reliable, noninvasive alternative to arterial blood–gas analysis for monitoring oxygen tension.

The pulse oximeter, which has become clinically available recently, measures SaO$_2$ continuously and noninvasively. Its probe, usually applied to a fingertip, senses changes in light absorption that occur synchronously with arterial pulsation. Thus the oximeter detects arterial rather than capillary hemoglobin saturation (SaO$_2$), on a beat-to-beat basis, without heating or arterialization (8). Previous investigations have established that the pulse oximeter accurately reflects SaO$_2$ in all age groups, with various hematocrits and in various body positions, over a range of 70–100% (8). We confirmed these findings in our laboratory before beginning this study. The accuracy of pulse oximetry has also been reported in preterm infants with fetal hemoglobin (12). No user calibration is required (8). The reliability of pulse oximetry can be affected by conditions that reduce vascular pulsation in the fingertip, such as hypothermia of more than several degrees centigrade, hypotension of less than 50 mm Hg mean arterial pressure in adults, and the

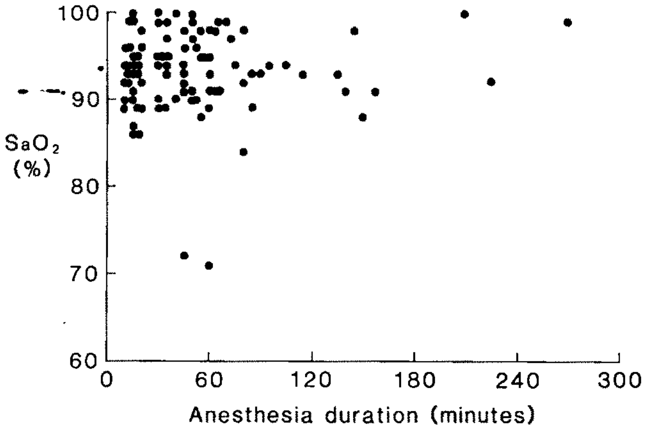

Figure 2. SaO_2 measured on arrival in the postanesthesia recovery room (ordinate) plotted against age (abscissa). There is no correlation ($P > 0.1$) between the two.

use of vasoconstrictive drugs (8). None of these conditions occurred in this study.

Our study was limited to otherwise healthy infants and children (ASA I), most of whom were day-surgery patients for relatively simple surgical procedures. Such patients do not ordinarily receive supplemental O_2 in the recovery room in our institution. Yet we found significant oxygen desaturation (an average SaO_2 equivalent to PaO_2 of 66 mm Hg) on arrival in the recovery room, despite the administration of 100% oxygen to all patients in the operating room just before their transport to the recovery room. Approximately 43% of these patients had moderate to severe hemoglobin desaturation, with an estimated PaO_2 at or below 60 mm Hg, at which level the hypoxic ventilatory response becomes prominent in awake human adults (13). In two patients, 2 and 5 yr old, SaO_2 decreased to the low 70s, indicating that their PaO_2 was below 40 mm Hg. Neither of these two children was noticeably cyanotic, probably owing to their relatively low hemoglobin concentrations (10.0 and 12.0 g/dl, respectively). Their heart rates (118 and 114 beats/min, respectively) were regular and similar to those of the normoxic children. One of these children had mild upper airway obstruction (light snoring) but appeared to be breathing adequately. He was given O_2 by mask, which increased SaO_2 to 100%. A second reading was taken in room air 6 min later, when he was awake and calm. His SaO_2 stabilized at 90% and the O_2 mask was put in place again. The second patient was breathing adequately, without upper airway obstruction, but despite severe hypoxemia here ventilation was not increased (transcutaneous PCO_2, 41–42 mm Hg). She was maintained on supplemental O_2, and a second reading in room air was not taken. The lack of hypoxic response may have been due to depression of the carotid chemoreceptors (14) by a trace amount of inhalation anesthetics, as has been described in adult patients (15,16).

An interesting and clinically important finding in this study was the relation between the state of wakefulness in the recovery room and the rate of recovery of pulmonary gas exchange. In patients who awoke promptly, whether crying or calm and alert, SaO_2 increased rapidly from the initial arterial hemoglobin desaturation. In contrast, in those who remained asleep, the recovery of hemoglobin saturation was protracted. Our study was limited to the intermittent measurement of SaO_2 during the immediate postanesthetic period. Further studies are needed to determine the duration of postanesthetic hemoglobin desaturation in children.

There are a number of possible causes for the postanesthetic increases in $P(A\text{–}a)O_2$ we observed. General anesthesia is associated with an 8–25% reduction in FRC, even in healthy young adult patients. (2,5,17–20). In children, FRC is further decreased during anesthesia (21), probably because the elastic recoil pressure of the lung is low (22,23) and closing capacity is increased (11). Thus in children a reduction of FRC would result in more profound airway closure and increase in $P(A\text{–}a)O_2$ during general anesthesia, which may continue into the postanesthetic period.

Anesthetics and narcotics depress the ventilatory response to CO_2 and may cause hypoxemia secondary to hypoventilation and hypercapnia (24). Upper airway obstruction may also cause hypoventilation, because anesthesia, in addition to its direct depressive effect on the respiratory centers, diminishes the response to hypoxemia and hypercapnia in the presence of partial airway obstruction (25). Furthermore, depletion of body CO_2 stores by prolonged artificial hyperventilation during anesthesia may result in hypoventilation in the postanesthetic period (posthyperventilation hypoventilation), which may in turn cause hypoxemia (26). A residual effect of inhalation anesthetics on hypoxic pulmonary vasoconstriction may persist and cause an increase in $P(A\text{–}a)O_2$ in the postanesthetic recovery room (27). It was probably not a major contributing factor in the present study; there was no statistically significant difference in the extent of hemoglobin desaturation between the group given inhalation anesthesia and those given primarily N_2O–narcotic anesthesia.

Because of their increased susceptibility to airway closure, it was expected that hemoglobin desaturation might be more severe in the infants than in the older children, but the data do not indicate such a trend. There are several possible explanations. First, infants

Table 2. Effect of State of Wakefulness in the Postanesthetic Recovery Room on SaO_2 (mean ± SEM) as Measured with Pulse Oximetry

Group	Period	n	State	SaO_2 (%)	Increase in SaO_2 (%)
Continued to sleep	PAR-1[a]	47	Asleep	92.9 ± 0.55	0.98 ± 0.45
	PAR-2[b]	47	Asleep	93.9 ± 0.40	($P < 0.05$)
Awoke in PAR	PAR-1	21	Asleep	91.5 ± 1.19	4.05 ± 1.12
	PAR-2	21	Awake	95.5 ± 0.71	($P < 0.01$)
Difference between groups					($P < 0.02$)

[a] PAR-1, on arrival in postanesthetic recovery room.
[b] PAR-2, 5–15 min later in postanesthetic recovery room.

were given much lower concentrations of inhalation anesthetics, usually less than 0.5% of halothane in the N_2O–O_2 mixture for maintenance of anesthesia. The infants recovered from anesthesia more rapidly than did the older children. Second, infants were often given disproportionately large tidal volumes, particularly when inexperienced trainees failed to reduce positive pressure to accommodate the more compliant respiratory systems in infants. Furthermore, a recent study (28) has shown that the time constant of the respiratory system for passive exhalation is longer in infants than in adults. Because infants breathed or were ventilated with high respiratory frequencies, the end-expiratory volume might not have returned to the true FRC, or relaxation volume. Thus, this inadvertent positive end expiratory pressure (PEEP) may have kept the FRC high and prevented airway closure. On the other hand, the lack of correlation between age and postanesthetic hemoglobin desaturation may indicate that PaO_2 was indeed underestimated in infants less than 6 weeks of age; in this age group the presence of a substantial concentration of fetal hemoglobin lowers P_{50} and impedes blood O_2 unloading at the tissue level (6,29). Therefore, hypoxemia in infants may be more profound than the levels estimated from a nomogram, which does not take the difference in O_2–hemoglobin affinity into account (9).

What is the clinical significance of the degree of hemoglobin desaturation we observed in healthy infants and children after general anesthesia? Patients with chronic pulmonary disease live with PaO_2 less than 60 mm Hg. Children with right-to-left shunting from congenital heart disease survive with PaO_2 in the 40s. Furthermore, natives at extreme high altitudes sustain complete life cycles at PaO_2 well below 60 mm Hg. The major difference between these cases of chronic hypoxemia and the children with acute hypoxemia in the current study is that in chronic hypoxemia a number of adaptive mechanisms develop, such as an increase in alveolar ventilation and cardiac output, a higher concentration of hemoglobin, and an increase in organic phosphates with a resultant reduction in oxygen affinity of hemoglobin that facilitates O_2 unloading at the tissue level (30). In contrast, children in the postanesthetic recovery room with acute hypoxemia not only lack adaptive mechanisms, but at the same time are deprived of normal protective mechanisms such as the hypoxic ventilatory response. Thus it is probable that these patients have an increased risk of potentially serious complications. It is common practice to give a minimum of 30% O_2 during general anesthesia, even when ventilation is assisted or controlled, to prevent hypoxemia. The present study shows that in children 21% O_2 (room air) is also a potentially hypoxic mixture during the early postoperative period. In many children's hospitals and university hospitals in the United States, supplemental oxygen is not routinely given to children in the postanesthetic recovery room. Cost may be a factor, but more important reasons appear to be ignorance and, because children often do not tolerate a face mask, "convenience." The present data indicate that the oxygen mask should be used at least until a child is awake enough to reject it, when the need for supplemental oxygen diminishes.

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The Half-Life of 2-Chloroprocaine

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The purpose of this study was to examine the discrepancy between the reported in vitro half-life of chloroprocaine and the slower observed disappearance of the drug in maternal plasma. The study had two aims. The first was to redetermine the in vitro half-life of 2-chloroprocaine in maternal and fetal plasma. The second was to determine the apparent half-life of 2-chloroprocaine in vivo after intrapartum epidural anesthesia in obstetric patients. Gas chromatography or gas chromatography/mass spectrometry techniques were used to measure 2-chloroprocaine in maternal or fetal plasma. Mean in vitro half-lives of 11.2 ± 2.8 and 15.4 ± 5.2 sec were found for maternal and fetal plasma from nine patients, respectively. The maternal half-life was significantly shorter than the fetal half-life ($P < 0.05$). The mean apparent in vivo half-life in maternal plasma was found to be 3.1 ± 1.6 min. The results of this study show that the half-life in vitro is correctly measured in seconds. However, the apparent half-life in vivo after epidural anesthesia is 3.1 ± 1.6 min and ranges from 1.5 to 6.4 min. The differences in the magnitude of the two findings is probably due to continuous uptake of the drug from the epidural space.

Key Words: ANESTHETICS, LOCAL—2-chloroprocaine. ANESTHESIA—obstetric.

2-chloroprocaine (nesacaine®) is an ester-linked local anesthetic agent rapidly hydrolyzed by plasma cholinesterases to inactive metabolites. Because of its rapid hydrolysis, its pharmacology has not been thoroughly studied. Until recently, 2-chloroprocaine could not be measured in plasma in vivo, so that its half-life had been determined only in vitro (1). In that study, the half-life in maternal and fetal cord plasma was reported to be 21 and 43 sec, respectively. However, these data are inconsistent with recent reports of measurable plasma levels in maternal and cord blood after epidural anesthesia or paracervical blockade (2,3). Graphs of 2-chloroprocaine plasma concentration vs time have been demonstrated repeatedly (2–4). Furthermore, in some cases levels are detectable for up to 30 min.

The reason for the discrepancy between the in vitro half-life data and the in vivo observations is not clear, but may have been due to methodological problems. The original study used techniques which were relatively insensitive and reported that 2-chloroprocaine was undetectable in maternal or fetal plasma (1). This was subsequently disproved (2–4). The difference between the very short half-life obtained in vitro and the persistence in vivo might also be due to slower uptake of the drug from the injection site. Furthermore, there may be inhibition of the enzyme by the large amount of substrate (5). Finally, the discrepancy may be due to a combination of several of the above factors.

The purpose of this study was to resolve the discrepancy between the reported in vitro half-life of 2-chloroprocaine and the slower disappearance of 2-chloroprocaine in maternal plasma in vivo. In order to accomplish this, the study had two aims. The first was to redetermine the in vitro half-life of 2-chloroprocaine in maternal and fetal plasma. The second was to estimate the half-life of 2-chloroprocaine in vivo after intrapartum epidural anesthesia in obstetric patients.

Methods

Patient Selection

Eighteen parturients were studied. Appropriate informed consent was obtained, and the study was ap-

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proved by the Human Investigation Committee of Cleveland Metropolitan General Hospital. Patients with hepatic or renal disease and those with histories of drug addiction were excluded from the study. Patients with mild complications of pregnancy, such as gestational diabetes or mild preeclampsia, were not excluded as long as epidural anesthesia was judged to be clinically appropriate by the attending physician.

Anesthesia

Different local anesthetic agents were used for each of the parts of the study. Patients who did not receive 2-chloroprocaine or any other compound metabolized by plasma cholinesterases before delivery were recruited for the in vitro study, and those who received 2-chloroprocaine for epidural anesthesia were recruited for the in vivo half-life study.

Sample Collection for In Vitro Half-Life Study

For the in vitro half-life study, 40 ml of maternal blood was collected from patients who did not receive chloroprocaine for epidural anesthesia. At delivery, both a doubly clamped section of cord and the placenta were obtained. As much fetal blood as possible (10–30 ml) was collected from the cord and by cannulating the placenta. The samples were immediately poured into a beaker containing 10 μl of liquid heparin (1000 usp unit/ml; Elkins-Sinn, Inc., Cherry Hill, NJ) per ml whole blood.

While the sample was stirred, 1 μl of 1 mg/ml 2-chloroprocaine per ml of blood was rapidly added to the beaker. After addition of the drug, 2 ml aliquots of blood were removed from the beaker at intervals depending upon how much blood was available. These intervals were 2, 10, 20, 30, 40, 50, 60, 75, 90, and 105 sec, and every 10–20 sec thereafter. Prior to the experiment, one sample was placed into a plain vacutainer, and the rest were placed into tubes containing 0.3 ml of the cholinesterase inhibitor, echothiophate iodide, (0.2 g/ml) (Ayerst Laboratories) (1,2,4). Samples with inhibitor were analyzed for 2-chloroprocaine, and the sample in the plain tube was analyzed for cholinesterase activity. Each tube was centrifuged, and the plasma was frozen for subsequent enzyme or drug analysis.

Sample Collection for the In Vivo Study

For the in vivo half-life portion of the study, maternal blood samples (3 ml) were collected intrapartum from an indwelling cannula in a superficial vein on the dorsum of the hand 1, 3, 5, 7, 10, 20, 30, 45, and 60 min after epidural anesthesia with 2-chloroprocaine, and at delivery. If a repeat dose was given, the sampling protocol was restarted. The drug was administered after a test dose using standard precautions to avoid either intrathecal or intravenous injection. The amount and timing of anesthesia were not influenced by this study. All samples were immediately stored on ice and analyzed as before.

Table 1. Clinical Characteristics—Mothers

	Study	
	In vitro half-life (n = 9)	In vivo half-life (n = 9)
Maternal age	28.4 ± 8.3	27.6 ± 3.2
Gravidity	3.6 ± 2.2	2.9 ± 1.7
Parity	2.0 ± 1.9	1.7 ± 1.3
Delivery method		
Vaginal	5	3
Repeat cesarean section	4	6
Complications		
Weight > 200 lbs	1	—
Weight < 100 lbs	1	—
Mild/moderate preeclampsia	1	—
Diabetes class A	—	3
Diabetes class C	—	1
Cholinesterase deficiency (heterozygote)	—	1

Specimen Analysis

Most of the plasma levels of 2-chloroprocaine were analyzed by single-ion-monitoring gas chromatography/mass spectrometry (4). Levels from several early patients were obtained by gas chromatographic techniques (2). The sensitivity of these methods are < 1 and < 3 ng/ml of plasma, respectively. The analytic technique does not influence determinations of drug disappearance. Plasma cholinesterase activity and the dibucaine number were determined by spectrophotometry for documentation of normal cholinesterase levels in all patients (6).

Estimation of Half-Life

Half-lives were estimated using the formula for exponential curve fitting, $y = ae^{-bx}$ where y equals the concentration of drug; a, the extrapolated zero-time concentration; e, the natural logarithm; b, the rate constant for drug disappearance; and x, the time in seconds or minutes (7). Half-life was then calculated by dividing 0.693 by b, the rate constant for drug

Table 2. Amount and Timing of Anesthesia for Patients Receiving 2-Chloroprocaine for Epidural Anesthesia

2-Chloroprocaine	Mean ± SD	Range
Number of doses administered	1.9 ± 1.1	1–4
Dosage administered (mg)	643 ± 289	220–990
Drug-to-delivery interval (min)		
First dose	51 ± 40	24–148
Last dose	23 ± 3	7–39

Table 3. Clinical Characteristics—Neonates

	Study	
	In vitro half life (n = 9)	In vivo half life (n = 9)
Gestational age (weeks)	39.4 ± 1.3	38.4 ± 1.7
(range)	(38–42)	(36–42)
Birthweight (g)	3411 ± 428	3499 ± 563
(range)	(2860–4090)	(2370–4120)
Apgar score		
< 7 at 1 min (number of neonates)	3	0
< 7 at 5 min (number of neonates)	0	0

disappearance. A single-compartment model was assumed. A minimum of three data points from a linear portion of the concentration–time profiles was used. The coefficient of determination (R^2) was used to test the goodness of fit of the model to the data. A minimum coefficient of determination of 0.90 was required for inclusion of patient data in the in vivo study (in the in vitro study, linearity was not a problem). Calculations and statistics were done with the statistical and curve-fitting programs for a Hewlett–Packard 41C programmable calculator. Semilogarithmic concentration–time plots showing the disappearance of 2-chloroprocaine in vitro or from maternal plasma were obtained by plotting concentrations of drug against time.

Statistical Analyses

Both pooled and paired t-tests were used to test whether or not there were differences in in vitro half-lives between maternal and fetal blood.

Results

Patient Population

The clinical characteristics of the parturients and the timing and amount of anesthesia are shown in Table 1 for each part of the study. Each group's antenatal characteristics were similar. One patient in the in vivo half-life subgroup was a class C diabetic, and another patient in this subgroup was identified as heterozygous for an abnormal plasma cholinesterase gene. Initially, the data from these patients were treated separately. However, when it became obvious that their 2-chloroprocaine half-life and enzyme activity were normal, they were included with the rest of the group. The mean value does not change if these two patients are included or excluded.

The amount and timing of anesthesia for the group who received 2-chloroprocaine for epidural anesthesia are shown in Table 2; the clinical characteristics of the neonates of these mothers are shown in Table 3. Only plasma from neonates in the in vitro half-life group was studied. In this group, all infants were at term and appropriate, or large, for gestational age. One infant had transient tachypnea in the nursery. All infants had Apgar scores > 7 at 5 min of life.

In Vitro Half-Life

The data for maternal and fetal in vitro half-lives of 2-chloroprocaine, goodness-of-fit values, and number of points studied are shown in Table 4. Both mean and individual values are presented. Maternal half-life values ranged from 6.9 to 15.4 sec, and fetal values ranged from 10.5 to 22.3 sec. Mean values were 11.2 ± 2.8 and 15.4 ± 5.25 sec for maternal and fetal plasma, respectively. Although samples were collected in some cases for as long as 240 sec, 2-chloroprocaine was nondetectable by 90 sec in most of the samples. The coefficient of determination values for fetal data ranged from 0.96 to 1.0 with a mean of 0.99 ± 0.01. In most cases, maternal drug half-life was found to be shorter than fetal drug half-life. The difference between mean half-life values for maternal and fetal plasma were significant by pooled t-test (t = 2.17; $P < 0.05$) and also by paired t-test (t = 4.27; $P < 0.05$) for a two-sided analysis. The coefficient of determination values for the maternal data ranged from 0.94 to 1.0 with a mean of 0.97 ± 0.02.

In Vivo Half-Life

In vivo half-lives were calculated from linear portions of plasma concentration–time profiles obtained after epidural anesthesia. Linearity was verified by goodness-of-fit calculations. Examples of two plasma concentration–time profiles are shown in Figures 1 and 2. The shape of these curves is very variable (2,4), although Figure 1 is similar to one that was published

Table 4. In Vitro 2-Chloroprocaine Half-Life (sec), the Coefficient of Determination (R^2), and the Number of Data Points Used

	$t_{1/2}$ Maternal	R^2 (Number of points)	$t_{1/2}$ Fetal	R^2 (Number of points)
Subject number				
1	15.2	0.94 (8)	22.4	0.99 (7)
2	8.8	1.00 (4)	11.2	0.99 (4)
3	9.3	0.97 (7)	21.7	0.99 (5)
4	15.4	0.96 (7)	16.9	0.99 (8)
5	11.8	0.95 (6)	10.5	0.98 (3)
6	10.8	0.98 (5)	21.7	0.98 (6)
7	10.8	1.00 (6)	11.8	1.00 (6)
8	6.9	0.95 (5)	11.0	0.96 (6)
9	11.6	0.95 (4)	11.8	0.99 (9)
Mean ± SD	11.2 ± 2.8	0.97 ± 0.02 (5.8 ± 1.4)	15.4 ± 5.2	0.99 ± 0.01 (6.0 ± 1.9)

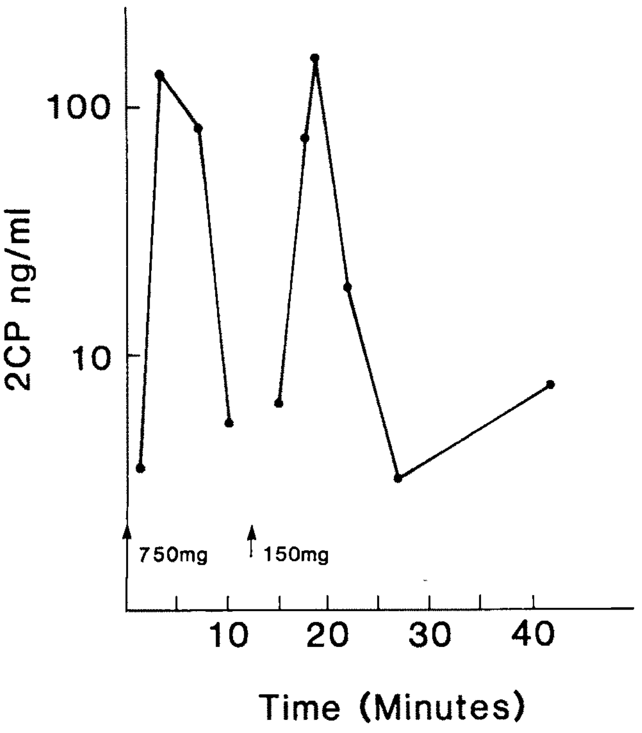

Figure 1. Plasma concentration–time profile illustrating uptake of 2-chloroprocaine from the epidural space.

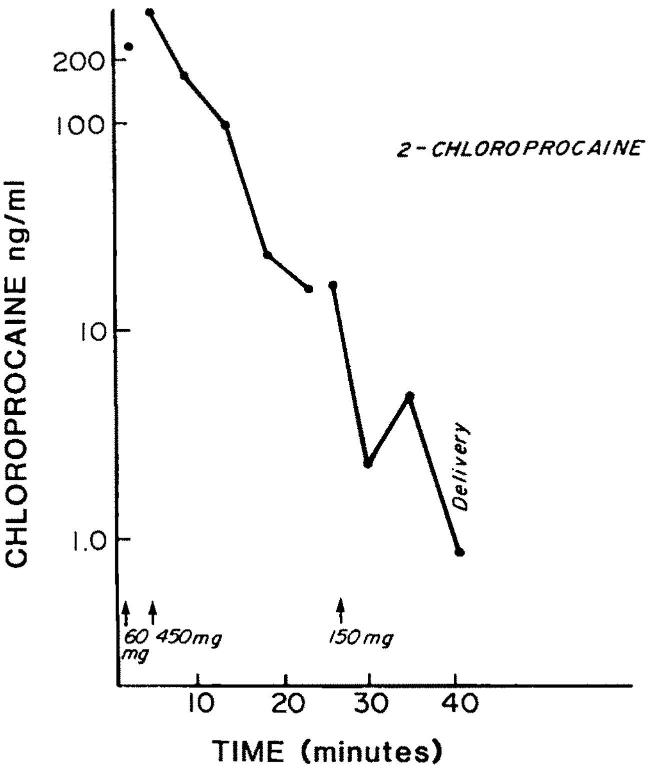

Figure 2. Plasma concentration–time profile from a patient heterozygous for the abnormal plasma cholinesterase allele.

previously (4). Others have been published earlier. Figure 1 illustrates a patient who received two doses of 2-chloroprocaine for a repeat cesarean section. Peak concentrations occurred several minutes after each administration of the drug. These appear to illustrate uptake of the drug from the epidural space at a rate initially more rapid than hydrolysis of the drug by plasma cholinesterases. A slight rebound is also noted at 40 min, which may have been due to physiologic changes accompanying the delivery at this point. The apparent rebound may be the result of methodological error, but this is an unlikely possibility. Half-lives were calculated from the decreasing portions of the curves which were present after each dose. The half-life for this patient (1.5 min) was the same after each dose. However, the coefficient of determination (which reflects the goodness of fit) 0.96, obtained after the second dose, reflected the more linear appearance of this curve. The coefficient of determination of the first disappearance was 0.81. Figure 2 illustrates a patient where the second dose had less of an influence on the plasma levels than in Figure 1. This patient was

Table 5. In Vivo 2-Chloroprocaine Half-Life (min), the Coefficient of Determination (R^2), and the Number of Data Points Used

	$t_{1/2}$ Maternal	R^2 (Number of points)
Subject number		
1	2.2	0.90 (5)
2	6.4	0.99 (3)
3	3.1	1.00 (3)
4	4.5	1.00 (3)
5	2.1	1.00 (3)
6	4.1[a]	0.97 (5)
7	1.5[b]	0.96 (3)
8	2.2	0.90 (4)
9	1.6	0.90 (3)
Mean ± SD	3.1 ± 1.6[c]	0.96 ± 0.05 (3.6 ± 0.9)

[a] Heterozygous for abnormal pseudocholinesterase allele dibucaine number 43; enzyme activity within normal range.

[b] Diabetic class C.

[c] Mean ± SD = 3.2 ± 1.7 without patients 6 and 7.

found to be heterozygous for an abnormal plasma cholinesterase allele (dibucaine number 43). However, her enzyme activity was normal. Her 2-chloroprocaine half-life was 4.1 min; the coefficient of determination was 0.97.

The data for maternal in vivo half-lives of 2-chloroprocaine after epidural anesthesia, the coefficient of determination, and the number of samples available for calculation of half-lives are shown in Table 5. Both mean and individual values for the nine patients are shown. Maternal drug half-life values ranged from 1.5 to 6.4 min with a mean value of 3.1 ± 1.6 min. The mean is 3.2 min with patients 6 and 7 excluded. Coefficients of determination values ranged from 0.90 to 1.0 with a mean of 0.96 ± 0.05.

Discussion

The results of this study suggest that the in vitro half-life is correctly measured in seconds; however, the apparent half-life in vivo after epidural anesthesia ranges from 1.5 to 6.4 min. The difference in the magnitude of the two findings is probably due to continuous uptake of the drug from the epidural space.

Based on previous family history, one patient was identified by the anesthesiologist as possibly having a gene for abnormal plasma cholinesterase. In our laboratory, this patient was subsequently identified as a heterozygote by the dibucaine number. Interestingly, this patient had a normal 2-chloroprocaine half-life and enzyme activity. Furthermore, this patient had neither adverse reaction to epidural anesthesia with 2-chloroprocaine, nor a prolonged epidural block. In this patient the one normal gene apparently coded for enough enzyme to metabolize 2-chloroprocaine in a manner similar to patients homozygous for the normal enzyme. This is very different from a previously reported patient who was homozygous for the abnormal gene, and who had excessive somnolence and a prolonged epidural block after epidural anesthesia (8).

The mean in vitro half-lives of 11.2 and 15.4 sec for maternal and fetal plasma, respectively, are slightly less than those of 21 and 43 sec reported previously by O'Brien et al. (1). This difference could result from differences in handling of the samples, in the sampling protocol, or in the analytic techniques. In the present study, the more rapid half-life obtained could have occurred because the experiments were run immediately after obtaining the samples. This is supported by the large standard error of the earlier study's values (2.21 and 4.24 sec for maternal and fetal plasma, respectively) compared with the present study (0.93 and 1.74 sec, respectively). Another reason for the differences between this study and the previous one may have been the sampling protocol: a larger sample size tends to improve the goodness of fit. Nevertheless, both studies agree that the in vitro half-life of 2-chloroprocaine is very short, and that the maternal drug half-life is significantly shorter than the fetal.

This study appears to be the first estimation of an in vivo half-life for 2-chloroprocaine after epidural anesthesia. Ideally, half-lives are determined after intravenous administration. However, if the drug is not given by this route, the half-life after epidural anesthesia is relevant. Clearly, the mean half-life of 3.1 min obtained after epidural anesthesia reflects what happens clinically more closely than does the in vitro half-life. Traditionally, with a two-compartment model, a distribution and an elimination half-life are obtained. The half-lives reported here assume a single compartment. Except for one case (2), no distribution phase was apparent after epidural anesthesia with chloroprocaine. This is probably because the drug is metabolized in the plasma (i.e., in the "distribution" compartment).

The large range of in vivo half-lives (1.5–6.4 min) was not found for the in vitro half-lives. This large range suggests that the variation may be due more to the differences in uptake of the drug from the epidural space than to differences in ability to metabolize the drug. This in turn reflects variations in the vascularity of the epidural space as well as placement of the epidural catheter. In some cases, the drug levels peak immediately after each dose (2), and in others the drug takes several minutes to reach its maximum level (4) (Figure 1).

In previous studies, 2-chloroprocaine was not always detectable in maternal plasma for an extended period of time after epidural anesthesia (2). In these patients with only isolated data points, a half-life could not be calculated. One can hypothesize that these patients have extremely rapid half-lives. Alternatively, the technique's sensitivity may have been less, or the uptake of the drug from the epidural space slower, so that enzyme hydrolysis could keep up with the appearance of the drug in plasma. The small range of the in vitro half-lives (6.9–15.4 sec) supports this latter hypothesis.

The short half-life of 2-chloroprocaine in maternal and fetal plasma (21 and 43 sec) has been suggested as evidence for its lack of toxicity (1). This rapid metabolism was assumed to result in undetectable concentrations of drug in maternal plasma and no fetal exposure (1). This assumption was disproved with better analytic techniques (2–4). Measurable levels are present, and the drug does cross the placenta in its active form. However, these levels are very low and probably inconsequential to the mother and fetus with normal plasma cholinesterase activity. The results of this study show that the mean apparent maternal 2-chloroprocaine half-life after epidural anesthesia is not 21 sec, but 3.1 min.

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ANESTH ANALG 279
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Lidocaine Pharmacokinetics in Children during General Anesthesia

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FINHOLT DA, STIRT JA, DIFAZIO CA, MOSCICKI JC. Lidocaine pharmacokinetics in children during general anesthesia. Anesth Analg 1986,65:279–82.

In spite of the increasing use of intravenous lidocaine in the operating room, no pharmacokinetic data exist for intravenous lidocaine in children. We studied ten children, ages 0.5–3 yr, and eight adults to determine lidocaine pharmacokinetics during anesthesia with halothane, nitrous oxide, and oxygen. After induction of anesthesia, tracheal intubation, and insertion of venous and arterial catheters, lidocaine, 1 mg/kg, was infused intravenously over 30 sec. Arterial samples were drawn at 0.5, 1, 2, 4, 5, 10, 15, 30, 60, 90, and 120 min. Plasma was separated and analyzed for lidocaine, using gas chromatography. Plasma concentration vs time data were fitted to a two-compartment model. Using standard formulas, we derived the following data: Children: distribution half-life ($t_{1/2}\alpha$) *3.2 min, elimination half-life* ($t_{1/2}\beta$) *58 min, volume of the central compartment* (V_1) *0.22 L/kg, volume of distribution (Vd area) 1.1 L/kg, and total plasma clearance (Cl) 11.1* $ml{\cdot}kg^{-1}{\cdot}min^{-1}$*. Adults:* $t_{1/2}\alpha$ *3.6 min,* $t_{1/2}\beta$ *43 min,* V_1 *0.16 L/kg, Vd area 0.71 L/kg, and Cl 9.8* $ml{\cdot}kg^{-1}{\cdot}min^{-1}$*. No significant differences were found between children and adults for all parameters analyzed. We conclude that children older than 6 months of age distribute and eliminate intravenous lidocaine in the same manner as adults.*

Key Words: ANESTHESIA—pediatric. ANESTHETICS, LOCAL—lidocaine. PHARMACOKINETICS—lidocaine.

Intravenous lidocaine is used in adults in the operating room to eliminate cardiac arrhythmias (1), diminish cardiovascular responses to intubation (2), modulate intracranial hypertension (3), decrease reflex bronchoconstriction (4), and abate coughing (5). Pharmacokinetic data for intravenous lidocaine are available for adults and may be used to predict dosages and infusion rates.

Due to differences in body water distribution, blood volume, body composition, and drug binding (6), children may absorb, distribute, and eliminate drugs differently than adults. Studies in children indicate age-related differences in lidocaine pharmacokinetics but are based on subcutaneous (7,8), intratracheal (8), or caudal (8,9) administration. Since intravenous lidocaine is being used with increasing frequency in children in the operating room, we undertook this study to determine lidocaine pharmacokinetics after intravenous administration in young children during general anesthesia.

Methods

Ten children, aged 0.5–3 yr, weighing 4.5–14 kg, were studied. Eight adults, aged 18–51 years, weighing 48–82 kg, were studied for comparison. Patients were free of hepatic, renal, or cardiac disease; received no premedication; and required arterial pressure monitoring for anesthetic management. Surgical procedures were plastic, orthopedic, neurosurgical, or general surgical and did not involve major blood loss during the study period. The University of Virginia Human Investigation Committee approved the study. Informed consent was obtained from adults and from parents of the children.

After induction (children: methohexital, 25–30 mg/kg per rectum; adults: thiopental, 4–5 mg/kg intravenously), maintenance anesthesia was begun with halothane (1.5% inspired), nitrous oxide (70% inspired), and oxygen. If not done preoperatively, intravenous and arterial catheters were inserted. Pancuronium (0.1 mg/kg) was given intravenously, followed by endotracheal intubation and controlled ventilation.

Control blood samples were drawn, and lidocaine, 1 mg/kg, was infused intravenously over 30 sec. Arterial blood samples (children: 2 ml, adults: 3 ml) were obtained at 0.5, 1, 2, 4, 5, 10, 15, 30, 60, 90, and 120

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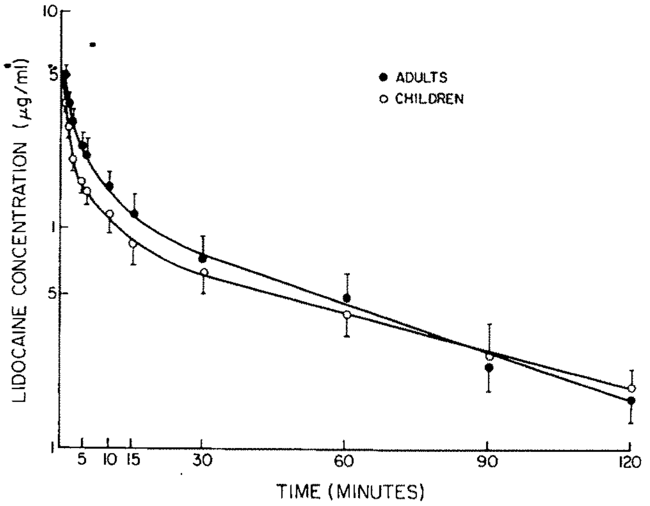

Figure 1. Lidocaine decay curves for children and adults (mean values at each time point). All patients were given lidocaine, 1 mg/kg intravenously.

min after lidocaine administration. Plasma was immediately separated and stored at −18°C for further analysis. Lidocaine concentrations were assayed in triplicate by gas chromatography (Varian 3700) as previously reported (10). The plasma concentration vs time data were fitted to both a two- and three-compartment model using nonlinear least squares regression analysis (11). Using standard formulas, we derived the following pharmacokinetic variables: distribution half-life ($t_{1/2}\alpha$), elimination half-life ($t_{1/2}\beta$), volume of the central compartment (V_1), volume of distribution (Vd area), and total plasma clearance (Cl). Mean values for these variables for each patient group were compared using Student's *t*-test for unpaired data. We considered differences significant if $P < 0.05$.

Results

Decay curves of lidocaine concentration vs time for children and adults are shown in Figure 1. A two-compartment model best fit our data with the following equations: Adults $Cp(t) = 4.92e^{-0.19t} + 1.22e^{-0.016t}$; children $Cp(t) = 3.66e^{-0.22t} + 0.88e^{-0.012t}$, where Cp(t) is plasma concentration at time t, and A and B are expressed in μg/ml.

Table 1 displays the derived pharmacokinetic parameters. We found no significant differences between adults and children for any of the parameters evaluated. The mean peak lidocaine level in the children was 3.67 μg/ml with a range from 2.37 to 4.54 μg/ml in 9 out of 10 patients. (One patient reached a level of 6.32 μg/ml).

Table 1. Derived Pharmacokinetic Variables for Lidocaine after Intravenous Bolus Administration

Variables	Children	Adults
$t_{1/2}\alpha$ (min)	3.2 ± 1.4	3.6 ± 1.2
$t_{1/2}\beta$ (min)	58 ± 19	43 ± 16
V_1 (L/kg)	0.22 ± 0.11	0.16 ± 0.09
Vd area (L/kg)	1.11 ± 0.34	0.71 ± 0.28
Cl ($ml\cdot kg^{-1}\cdot min^{-1}$)	11.1 ± 1.8	9.8 ± 1.4

Abbreviations: $t_{1/2}\alpha$, distribution half-life; $t_{1/2}\beta$, elimination half-life; V_1, volume of the central compartment; Vd area, volume of distribution; Cl, total plasma clearance.

All values represent mean ± SEM.

Discussion

Numerous investigators have determined intravenous lidocaine pharmacokinetics in healthy adult volunteers (12–15), in a variety of disease states (13,16,17), in conjunction with other drugs (18,19), and during general anesthesia (18,20,21) (Table 2).

Rational use of intravenous lidocaine in children dictates a need for similar pharmacokinetic data. Although data for intravenous lidocaine pharmacokinetics in children are not available, previous studies suggest there are age-related differences in lidocaine pharmacokinetics (Table 2). After intratracheal lidocaine (4 mg/kg), children under 3 yr of age achieved higher lidocaine levels (6.7–6.8 μg/ml) than children over 3 yr of age (3.2–4.6 μg/ml) (8). In the same study, caudal administration of lidocaine (4 mg/kg) showed no apparent age-related changes in plasma levels. A subjective review of decay curves indicates similar elimination rates for all ages studied. A more complete pharmacokinetic study after caudal lidocaine (5 mg/kg) in children 3–9 yr of age found a longer elimination half-life and larger volume of distribution than reported in adults (9). Similarly, neonates are reported to have large volumes of distribution and prolonged elimination of lidocaine (7,22). Twenty percent of a single lidocaine dose remains unabsorbed from the epidural space 2–4 hr after initial injection in adults (15). None of the pediatric studies included identically treated adult controls. Thus, interpretation and clinical application to intravenous administration is difficult.

Our study shows that lidocaine distribution and elimination in young children proceeds in the same manner as in adults (Table 2). Furthermore, in 9 out of 10 children, peak levels did not reach levels considered toxic in adults, and there were no apparent toxic reactions in this study. A 6-month-old child should have a mature central nervous system and cardiovascular system and normal plasma drug binding,

Table 2. Comparison of Lidocaine Pharmacokinetic Studies in Children and Adults

	$t_{1/2}\alpha$ (min)	$t_{1/2}\beta$ (min)	V_1 (L/kg)	Vd area (L/kg)	Cl (ml·kg^{-1}·min^{-1})
Adults (intravenous)					
Healthy volunteers					
Other studies (12–15)[a]	4.3–8.3	87–108	0.44–0.77	1.1–1.3	9.2–11.4
DiFazio[b]	3.9	56	0.89	1.87	11.1
General anesthesia					
Balanced	—	108	—	2.0	15.8
Halothane	—	124	—	1.7	10.7
Children					
Caudal (3–9 yr) (9)	—	155	—	3.05	15.4
Subcutaneous (neonates) (7)	—	190	—	2.75	10.0
This study (intravenous)					
Adults	3.6	43	0.16	0.71	9.7
Children (0.5–3 yr)	3.2	58	0.22	1.11	11.1

Abbreviations: $t_{1/2}\alpha$, distribution half-life; $t_{1/2}\beta$, elimination half-life; V_1, volume of the central compartment; Vd area, volume of distribution; Cl, total plasma clearance.

[a] Data converted to body weight basis for simplification using 70 kg as average adult weight.

[b] Unpublished data from this laboratory.

and thus should tolerate the same plasma lidocaine level as does an adult.

A decrease in lidocaine elimination may have been anticipated due to the use of halothane and controlled ventilation, known to decrease cardiac output and hepatic blood flow (23). Previous work in dogs (18,20) and humans (21) has found prolonged elimination and decreased clearance of lidocaine during halothane anesthesia. These investigators recommended decreasing lidocaine dosage during general anesthesia with halothaane (21). Our data in adults and children did not indicate decreased metabolism. Distribution and elimination half-lives, and plasma clearance are similar to data obtained in awake, unmedicated, human volunteers in this laboratory (unpublished data, Table 2).

In summary, we have shown that lidocaine pharmacokinetics following intravenous lidocaine during halothane–nitrous oxide anesthesia are similar in adults and children. In children above 6 months of age, it does not appear that lidocaine dose needs to be altered due to age alone.

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Double-Blind Comparison of Intravenous Doses of Dezocine, Butorphanol, and Placebo for Relief of Postoperative Pain

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GALLOWAY FM, VARMA S. Double-blind comparison of intravenous doses of dezocine, butorphanol, and placebo for relief of postoperative pain. Anesth Analg 1986;65:283–7.

The safety and efficacy of intravenous doses of dezocine (5 or 10 mg), butorphanol (1 mg), and placebo were compared in a double-blind study in 160 patients with moderate to severe postoperative pain. Analgesic efficacy was assessed for 6 hours after each dose. Mean pain relief scores were consistently higher, indicating greater pain relief, for the three active treatment groups than for the placebo group. The 10-mg dezocine dose was the most effective treatment, and 5 mg of dezocine was comparable to 1 mg of butorphanol. In the 2 hours after the first dose, 32% of the 10-mg dezocine group, 53% of the 5-mg dezocine group, 65% of the butorphanol group, and 88% of the placebo group withdrew from the study because of unsatisfactory pain relief. The differences in these percentages were statistically significant ($P < 0.05$) between each active therapy group and the placebo group, and between the 10-mg dezocine group and the butorphanol group. Changes in degree of sedation were similar in the three active therapy groups. Adverse reactions were rare, mild, and equally distributed among the four treatment groups. We conclude that 10 mg of dezocine is superior to 1 mg of butorphanol, and that 5 mg of dezocine is as effective as 1 mg of butorphanol for the relief of moderate to severe postoperative pain.

Key Words: ANALGESICS—dezocine. PAIN—postoperative.

Mixed agonist–antagonist opioid analgesics are considered safer than pure agonist opioids because of their ceiling effect for respiratory depression and their lower addiction potential. Dezocine (Wy-16,225), a synthetic bridged aminotetralin, is one of the newer compounds in this category (Fig. 1). In standard animal analgesic tests, dezocine was 7–18 times more potent than morphine with a therapeutic index greater than 1000 and had slightly less antagonistic activity than nalorphine (1,2). Dezocine produced substantially less respiratory depression and hypotension in dogs than did morphine and pentazocine, and it had no bronchoconstrictive and histamine-releasing activity (3). Dezocine did not suppress abstinence symptoms in morphine-dependent monkeys or produce physical dependence when administered chronically to monkeys (4). Studies in humans conducted at the Addiction Research Center in Lexington, Kentucky, have confirmed these observations (5).

The analgesic activity of parenterally administered dezocine has been compared with that of a placebo, morphine, and meperidine in patients with postoperative pain, renal colic, or chronic cancer pain (6–12). Intramuscular doses of 10 mg of dezocine were as effective as 10 mg of morphine and 50–100 mg of meperidine for the relief of postoperative pain (6–8). In most clinical trials, the onset of analgesia has been more rapid with dezocine than with meperidine and morphine, and the duration of action has been slightly shorter than that of morphine.

We studied butorphanol, an established mixed agonist–antagonist opioid analgesic (13), administered intravenously in the immediate postoperative period (14). In the present investigation, we compared intravenously administered dezocine and butorphanol in a double-blind, placebo-controlled study in patients with postoperative pain.

Materials and Methods

One hundred sixty male and female surgical patients between the ages of 18 and 70, classified as ASA physical status I or II, participated in this study, which was approved by the Denver Department of Health and Hospitals Independent Review Committee. Preg-

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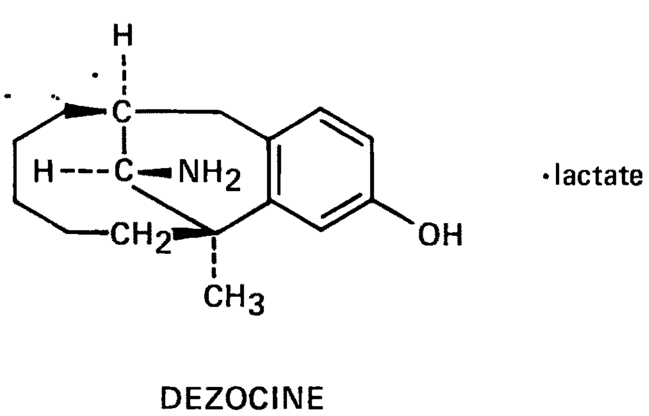

Figure 1. Chemical structure of dezocine.

nant women, patients sensitive to opioid analgesics, those requiring continuous opioid treatment during hospitalization, those chronically taking analgesics and psychotropic drugs, and those with a history of opioid abuse were excluded. Written informed consent was obtained from all patients.

The patients had intraabdominal, orthopedic, and general surgical procedures under general anesthesia. There were no restrictions on the drugs used for anesthesia. Premedication usually consisted of an anxiolytic (diazepam) and an anticholinergic (atropine) agent. For most procedures, anesthesia was induced by intravenous thiamylal and was maintained by inhalation anesthetic agents (enflurane, halothane, isoflurane) supplemented by skeletal muscle relaxants. In a few patients, anesthesia was supplemented by small doses of opioids.

After surgery, patients were randomly assigned to one of four treatment groups and received an intravenous injection of either dezocine (5 or 10 mg), butorphanol (1 mg), or a placebo. Patients were excluded if they had received an analgesic medication within 3 hr of the administration of the study drug.

All preanesthetic interviews and postoperative observations and assessments were conducted by the same blinded observer. Drug efficacy and safety evaluations were made 15, 30, and 60 min and 2, 3, 4, 5, and 6 hr after injection and were repeated after each subsequent dose. The patients assessed pain intensity at baseline and at each observation, and rated it as none, 0; mild, 1; moderate, 2; or severe, 3. They also evaluated pain intensity on a visual analog scale, from "no pain" to "worst pain ever felt," and rated the degree of pain relief as worse, −1; none, 0; a little, 1; moderate, 2; a lot, 3; or complete, 4, at all observation times.

Several measures of analgesic efficacy were derived from the patients' subjective evaluations of pain intensity and pain relief. The pain intensity difference and pain analog intensity difference scores were determined by subtracting the respective pain intensity score at each evaluation from the corresponding baseline pain intensity score. Cumulative or summed efficacy measures—the summed pain intensity difference score, the summed pain analog intensity difference score, and the total pain relief score—were determined as a weighted sum of the scores during each dosage interval (i.e., the sum of each score multiplied by the fraction of an hour since the last observation).

A maximum of six doses was to be allowed over 48 hr with at least 2 hr between doses. If pain relief was inadequate, a standard analgesic could be offered as soon as 15 min after study drug administration. The timing of such repeat medication, which resulted in elimination of the patient from the study, was recorded. These patients were assigned efficacy scores corresponding to baseline pain intensity or to "no relief" according to the standard convention (15,16).

Before drug administration and at each observation time, blood pressure, pulse, and respiratory rate were recorded, and the degree of sedation was noted as none (wide awake with no evidence of sedation), mild (awake with signs of drug activity), moderate (asleep, but arousable to verbal stimuli), or marked (asleep and nonresponsive to verbal stimuli). Any adverse experiences were recorded, and their relation to the study medication was judged. Laboratory tests (complete blood cell count, serum chemistry profile, and routine urinalysis) were done before the operation and within 24 hr of the end of the study.

At the end of the study, patients evaluated the overall effect of treatment (excellent, good, fair, or poor). The investigator also made an overall clinical judgment of whether the treatment was satisfactory, considering the degree and duration of analgesia and the presence or absence of adverse effects.

The demographic and baseline efficacy variables of a continuous nature were compared by one-way analysis of variance, supplemented by the Student–Newman–Keuls test for paired comparisons. Nominal variables and the frequencies of adverse effects were compared by the χ^2-test; Fisher's exact test was used for paired comparisons when appropriate.

Formal statistical comparisons were restricted to the initial dose period. Efficacy variables of an ordinal or nominal nature were analyzed by the generalized Cochran–Mantel–Haenzel procedure, using marginal ridit scores with the initial pain level as covariable (17). Pain analog intensity difference and summed pain analog intensity difference scores were compared among the groups by analysis of covariance. Vital signs and laboratory determinations were examined for changes within groups from baseline by a paired *t*-test, and comparisons among the groups were made by analysis of covariance.

Results

The study population consisted of 68 (42%) men and 92 (58%) women; the mean age was 32 yr (range, 18–70 yr) and the mean weight was 69 kg (range, 44.5–99 kg). Before receiving the first dose of study medication, 52 (32%) patients had moderate pain and 108 (68%) patients had severe pain. There were no statistically significant differences among the groups in demographic characteristics or baseline pain intensity.

Table 1 summarizes the mean changes from baseline in pain relief scores after the first dose of medication in the 160 patients who had valid efficacy data (one patient in the 5-mg dezocine group was excluded for having received meperidine less than 3 hr before the study drug). During the first hour after drug administration, the efficacy scores for the active treatment groups were all significantly higher ($P < 0.05$), indicating greater pain relief, than for the placebo group. The mean pain relief scores were highest for the 10-mg dezocine group, followed by those for the 5-mg dezocine and 1-mg butorphanol groups, which generally were similar. The 10-mg dezocine group had significantly ($P < 0.05$) greater pain relief than the 1-mg butorphanol and 5-mg dezocine groups from 30 min through 2 hr after drug administration. All three active treatments were superior to placebo, as indicated by significantly ($P < 0.05$) higher total pain relief scores. The results were similar on the other two scales.

Table 1. Mean Pain Relief Scores After the First Dose of Medication

	Treatment group			
Time	5 mg Dezocine (n = 39)	10 mg Dezocine (n = 41)	1 mg Butorphanol (n = 40)	Placebo (n = 40)
15 min	1.7^{a}	$2.6^{a,b}$	$2.4^{a,b}$	0.2
30 min	1.6^{a}	$2.5^{a,b,c}$	1.9^{a}	0.3
1 hr	1.3^{a}	$2.0^{a,b,c}$	1.3^{a}	0.3
2 hr	0.9^{a}	$1.4^{a,b,c}$	0.6	0.2
3 hr	0.6	0.8^{a}	0.6	0.3
4 hr	0.3	$0.5^{a,b}$	0.3	0.1
5 hr	0.2	0.2	0.2	0.1
6 hr	0.1	0.1	0.0	0.0
6 hr	3.7^{a}	5.1^{a}	3.1^{a}	0.8

Higher scores indicate greater relief.
[a] Significantly higher than placebo ($P < 0.05$).
[b] Significantly higher than 5 mg of dezocine ($P < 0.05$).
[c] Significantly higher than 1 mg of butorphanol ($P < 0.05$).

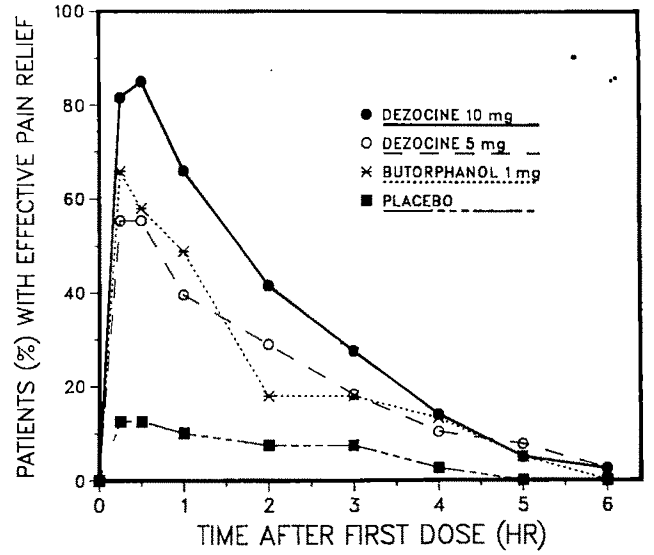

Figure 2. Percent of patients with at least moderate pain relief during the first observation period.

Effective pain relief, as indicated by a pain relief score of moderate or greater, was reported at some time during the initial dose period by 90% of the patients in the 10-mg dezocine group, 69% of the patients in the 1-mg butorphanol group, 69% of the patients treated with 5 mg of dezocine, and 13% of the placebo-treated patients (Fig. 2). The percentages of patients in the three active treatment groups with effective pain relief were significantly higher ($P < 0.05$) than those in the placebo group through the first hour after drug administration, and the differences continued to be statistically significant through 2 hr for the 5-mg dezocine group and through 3 hr for the 10-mg dezocine group. Moreover, the percentages of patients with effective relief in the 10-mg dezocine group were significantly higher ($P < 0.01$) than those in the 1-mg butorphanol group at 30 min and 2 hr, and significantly ($P < 0.05$) higher than those in the 5-mg dezocine group through the first hour after drug administration.

Formal statistical comparisons were restricted to the observation period after the first dose because of the high percentage of patients in each group who withdrew from the study during the initial dose period, and because the patients who remained received repeat medication when needed and not at set intervals.

No patient received the maximum of six doses, and only one patient (in the 5-mg dezocine group) remained in the study for the entire 48 hr. The mean number of doses administered was highest in the 10-mg dezocine group (1.5 doses), followed by the 5-mg dezocine group (1.3 doses), the 1-mg butorphanol group (1.2 doses), and the placebo group (1.1 doses).

The mean duration of study participation was 5.3 hr in the 10-mg dezocine group, 3.4 hr in the 5-mg dezocine group, 3.0 hr in the 1-mg butorphanol group, and 1.3 hr in the placebo group. Patients in the 10-mg dezocine group remained in the study significantly longer ($P < 0.01$) than did those in the placebo group.

After the first dose, 95% of the patients in the placebo group, 80% of the butorphanol and 5-mg dezocine groups, and 61% of the 10-mg dezocine group had withdrawn from the study. Of these, 88% of the patients in the placebo group were early therapeutic failures (i.e., required a standard analgesic within 2 hr of the initial dose), compared with 65% of the butorphanol-treated patients, 53% of the patients treated with 5 mg dezocine, and 32% of the patients treated with 10 mg dezocine. The percentage of early therapeutic failures was significantly ($P < 0.05$) lower in all three active therapy groups than in the placebo group, and in the 10-mg dezocine group (32% of the patients) than in the butorphanol group (65%). For the patients who remained in the study longer than 2 hr, regardless of the number of doses received, the reasons for study termination were nondrug related (e.g., preference for an oral medication, decreased requirement for a parenteral analgesic, intercurrent medical or surgical problems) in 15 of 27 (56%) patients in the 10-mg dezocine group, 7 of 17 (41%) in the 5-mg dezocine group, 9 of 13 (69%) in the 1-mg butorphanol group, and 2 of 5 (40%) in the placebo group. The differences between groups were not statistically significant.

In all four groups, mean sedation was mild at baseline. After drug administration, sedation increased to near moderate in the active therapy groups and remained unchanged in the placebo group. Both the sedation scores and the percentages of patients with an increased degree of sedation from baseline were significantly ($P < 0.01$) higher in each active therapy group than in the placebo group at 15 and 30 min. At 1 hr and beyond, the mean sedation levels in the active therapy groups were near or below baseline.

The most frequent adverse experience during the initial evaluation period was excessive or prolonged sedation, reported for two (5%) patients treated with 5 mg of dezocine, three (7%) patients treated with 10 mg dezocine, and one (3%) butorphanol-treated patient. The only adverse experiences observed during the subsequent evaluation periods were nausea and vomiting, reported by three of 16 (19%) patients in the 10-mg dezocine group and one of eight (13%) patients in the butorphanol group. No patient showed signs of clinically significant respiratory depression. There were no statistically significant differences among the groups in the frequencies of adverse effects during any evaluation period or throughout the entire study.

Table 2. Summary of Physician and Patient Overall Evaluations

	Treatment group			
Evaluation	5 mg Dezocine	10 mg Dezocine	1 mg Butorphanol	Placebo
Physician evaluation				
Satisfactory	11 (28%)	22 (55%)	9 (23%)	1 (3%)
Unsatisfactory	28 (72%)	18 (45%)	31 (78%)	39 (98%)
Patient evaluation				
Excellent	3 (8%)	3 (8%)	0 (0%)	1 (3%)
Good	7 (18%)	12 (30%)	9 (23%)	0 (0%)
Fair	7 (18%)	12 (30%)	7 (18%)	1 (3%)
Poor	21 (55%)	13 (33%)	23 (59%)	38 (95%)

No patient had clinically significant changes in vital signs. The results of laboratory tests, which were done before and after the study, showed no clinically significant changes from baseline that were attributable to therapy.

In both the patient and physician overall evaluations of the study drugs (Table 2), each active treatment group was given a rating that was statistically significantly higher than that for the placebo group, and 10 mg of dezocine showed a significant ($P < 0.05$) advantage over both 5 mg of dezocine and 1 mg of butorphanol.

Discussion

In this study, the onset of analgesia was equally rapid with both the dezocine doses and the butorphanol dose. The 10-mg dose of dezocine provided effective analgesia for up to 4 hr after administration, and the 5-mg dezocine and 1-mg butorphanol doses provided analgesia for up to 2 hr. In a previous study (14), we found 1 mg intravenous doses of butorphanol to have a similar duration of action. The analgesic effects seen with 5- and 10-mg dezocine doses were dose-dependent in both the degree and the duration of analgesia. This dose response has been reported with intravenous and intramuscular doses ranging from 5 to 20 mg (8,9,12).

The number of patient withdrawals in each treatment group may seem extremely high, but the reasons why must be considered and a differentiation should be made between early and late dropouts. According to the program, patients requiring repeat medication within 2 hr of the initial dose were considered therapeutic failures, given a standard analgesic, and withdrawn from the study. The reasons for withdrawal of the patients who remained in the study longer than 2 hr, regardless of the number of doses received, were often not drug related. Thus, although early discontinuations (less than 2 hr after initial dose) correlated with efficacy, late discontinuations tended to reflect the diminished need for an intravenous analgesic or a preference for an oral medication. Both the mean duration of study participation and the mean number of doses of test medication confirm the trends observed in the initial evaluation period. Patients treated with 10 mg of dezocine remained in the study longest and received the highest number of doses, followed by those who received 5 mg of dezocine, 1 mg of butorphanol, and placebo.

The results of this study show the safety and efficacy of dezocine for the treatment of moderate and severe postoperative pain. The 5- and 10-mg doses were equal and superior, respectively, to 1 mg of butorphanol in analgesic efficacy.

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1986;65:288–93

Special Article

Harvey Cushing:

His Contribution to Anesthesia

Nicholas P. Hirsch, MB, BS, FFARCS, and Gary B. Smith, BM, FFARCS

> Please put this [collection of Ether charts] in a corner of the Treadwell Library, where someday some young fellow may brush the dust from it and say, "Who were these fellows anyhow, and what is this 'ether' they are talking about? Do you mean that people used to be put to sleep by the inhalation of drugs in the 19th century?"
>
> *Harvey Cushing, 1920*

Cushing's earliest experience with anesthesia prompted an interest in it and led to many important contributions to the specialty, including the introduction of the first anesthetic charts and routine blood pressure measurement. In addition, he reintroduced the use of local anesthetics into clinical practice, coined the term "regional anaesthesia," and recognized that improvements in anesthetic standards could lead to better operating conditions.

On January 10, 1893, Dr. Frank Lynam offered Cushing, then a Harvard medical student, the opportunity to administer ether to a woman with a strangulated hernia. Lynam recalls that Cushing "was not as anxious for the position as I had expected. . . ." (1,p69). It is recorded in Cushing's "line-a-day" diary, and in a letter to his father, that he had given ether on several occasions before this date, and it appears that his reluctance on this day may have arisen from a previous unpleasant experience. Despite Cushing's reservations, the patient was anesthetized. The surgeon, Dr. C. B. Porter, found "a sack filled with gangrenous black intestines floating in pus. The patient failed rapidly and, though stimulation was given, died on the operating table a few minutes later" (1,p70).

In the early days of anesthesia, death under ether was not uncommon, and it is probable that the woman's death was not the first that Cushing had witnessed. This is substantiated by a letter written by him in February 1920 in which he describes his first experience administering ether (2). He recalls that he was called down from his seat in the surgical amphitheater and sent into a side-room, where, under the direction of an orderly, he proceeded to "etherize" the patient, an elderly man, as best he could. After repeated urgent calls from the surgeon, the patient was wheeled into the amphitheater. As the operation started, "there was a sudden great gush of fluid from the patient's mouth most of which was inhaled. . . ." The patient died. Cushing writes:

> I supposed that I had killed the patient. The operation was completed in spite of the episode, as a demonstration to the class. I slunk out of the hospital, walked the streets of North Boston the rest of the afternoon, and in the evening went to the surgeon's house to ask if there was any possible way I could atone for the calamity to the man's family before I left the Medical School and went into some other business.
>
> To my perfect amazement I was told it was nothing at all, that I had nothing to do with the man's death, that he had a strangulated hernia, and had been vomiting all night anyway, and that sort of thing happened frequently and I had better forget about it and go on with the Medical School. I went on with the Medical School but have never forgotten about it.

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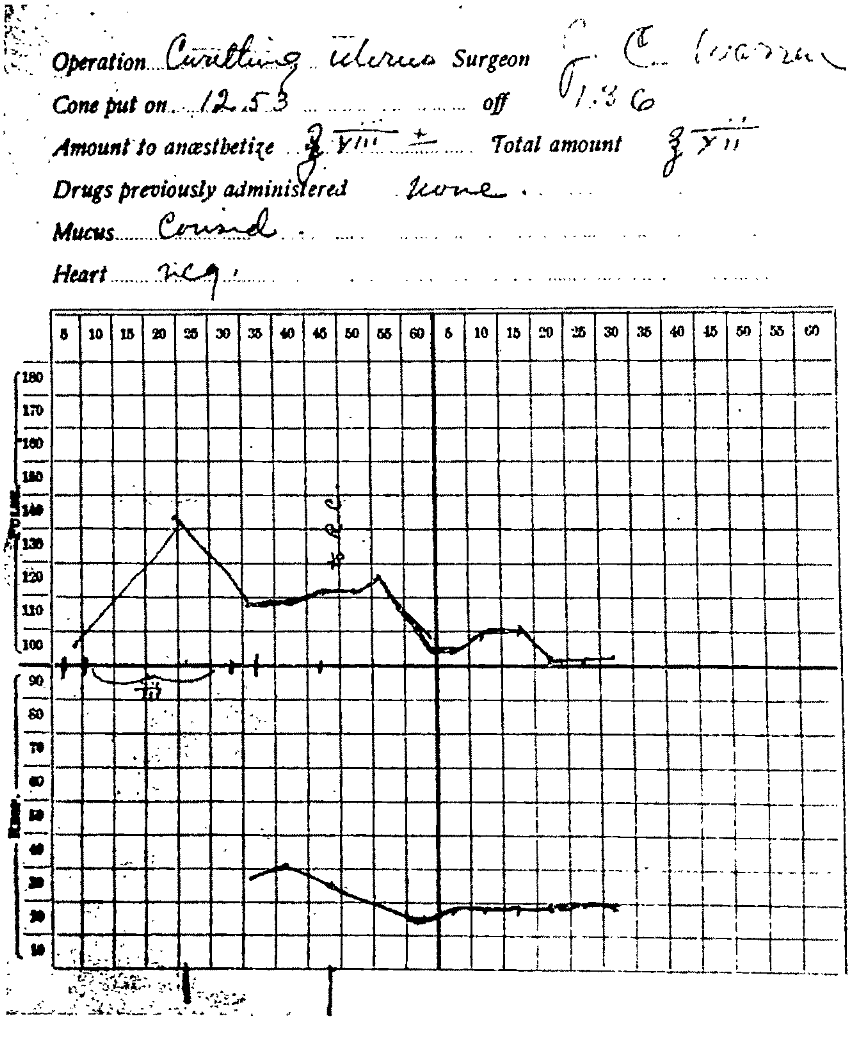
It is evident that these episodes had a profound effect on Cushing and probably contributed to his interest in making anesthesia a safer specialty.

Harvey Williams Cushing was born in Cleveland, Ohio, on April 8, 1869, the son of a doctor. After graduation from the Central High School in 1887, he entered Yale College and distinguished himself in both academia and athletics, obtaining his BA degree in June 1891. Despite several pleas by Russell Chittenden, Professor of Physiological Chemistry, for Cushing to remain at Yale, he decided to follow in his brother's footsteps and enter Harvard Medical School; he took up his place in September 1891. On June 26, 1895, he received the degrees of MD and AM cum laude.

It was during his second year as a medical student that Cushing gave that first fateful anesthetic. After this unfortunate episode, he and Ernest Amory Codman, a classmate, resolved that they would improve their technique of administering ether. Cushing suggested (2) that "in order to make a game of the task before us we made a wager of a dinner as to who could learn to give the best anaesthesia."

Codman, writing later (2), recalled nothing of the dinner of which Cushing spoke but remembers the "determination to train ourselves to be good etherizers." To this end they devised the first anesthetic records. These "ether charts" were introduced in 1894 and allowed both the anesthetist and the surgeon to follow the condition of the patient by recording pulse, respiration, and temperature during the operation (Fig. 1). There was no doubt in Cushing's mind (2) that "we both became very much more skillful in our jobs . . . particularly due, I think, to the detailed attention which we had to put upon the patient by the careful recording of the pulse rate throughout the operation." He also states (2) that careful anesthesia and record taking "was undoubtedly a step toward improvement in what had been a very casual administration of a dangerous drug. We do much better with ether these days, but even so there remains much to learn."



Operation Curetting uterus Surgeon E. A. Codman
Cone put on 12.53 off 1.36
Amount to anæsthetize ℥ viii ± Total amount ℥ xii
Drugs previously administered None.
Mucus Consid.
Heart reg.

Figure 1. One of Codman's early ether charts, dated November 30, 1894. (By permission of *Surgery, Gynecology and Obstetrics.*)

In April 1895, Cushing took a locum tenens position at the Massachusetts General Hospital and for two months worked with the surgeon John Wheelock Elliot. During this time Cushing assisted at two operations for brain tumor, and it appears that his enthusiasm for neurosurgery stems from this experience. His internship, at the same hospital, began on August 1 of that year, after which he moved to Baltimore to become assistant resident to William S. Halsted at the Johns Hopkins Hospital (Fig. 2). Halsted, who had also attended Yale, had moved to Baltimore from New York in 1886 and had become Professor of Surgery in 1890.

Anesthetic practice in Baltimore was similar to that in Boston where medical students were called upon to administer anesthesia using ether cones made from newspaper. Cushing found it impossible to change this practice, and after a number of anesthetic deaths at the hospital in the autumn of 1897, he began to investigate the use of cocaine as a local anesthetic. He became adept at performing nerve blocks for a number of surgical procedures, and later published his observations concerning "Cocaine Anaesthesia in the Treatment of Certain Cases of Hernia and in Operations for Thyroid Tumors"; this article appeared in the Johns Hopkins Hospital Bulletin in 1898 (3). It is obvious from this article that Cushing recognized the dangers of administering ether to those patients with "full stomachs" or to the elderly with respiratory or cardiovascular disease. Several other publications dealing with local anesthesia followed (4,5). These reports contain details of his technique of supplementing cocaine anesthesia with "a few inhalations of chloroform—not enough, however, to make the patient lose consciousness. . . ." Cushing continues, "We may justly speak, therefore, of the method of anaesthesia which is employed as a morphea–cocaine–chloroform combination, the first and last drugs being merely adjuvants of the local anaesthetic. . . ." He further describes the role of an assistant in place of the anesthetist who offers "timely encouragement" to the patient. Cushing was almost certainly the originator of the term "regional anesthesia" (6). Although there is little doubt that Cushing rekindled interest in the use of cocaine anesthesia, it is interesting to note that Halsted had experimented extensively with the drug shortly after its introduction in 1884, and had published his findings (7). However, Cushing claims (8) that he "was utterly unaware that his chief had ever made studies with cocaine of any sort, so reticent was he about this particular matter and so little did questions of priority interest him."

Figure 2. Harvey Cushing, age 29; photographed during his time at Johns Hopkins Hospital (Yale Medical Library).

During his residency at the Johns Hopkins Hospital, Cushing remained interested in neurosurgery, and in July 1900 he began 14 months of travelling in Europe visiting many eminent neurologists and neurosurgeons. While in Berne, under the direction of Theodore Kocher, his experiments led to the finding that an increase in intracranial pressure was associated with a reflex increase in the arterial blood pressure; this later became known as the Cushing reflex (9).

Shortly after concluding his work in Switzerland, Cushing visited the Ospidale di St. Matteo in Pavia where he found that a simple, "home-made" adaptation of Scipione Riva-Rocci's blood pressure device was in routine daily use by the bedside of every patient. He quickly sketched a diagram of the apparatus; this drawing can be found in his diary dated May 5, 1901 (Fig. 3). On his return to Baltimore in September of that year, Cushing almost immediately developed a new anesthesia chart (Fig. 4), and insisted that blood pressure should be recorded during all major operations. His first publications relating to the subject of

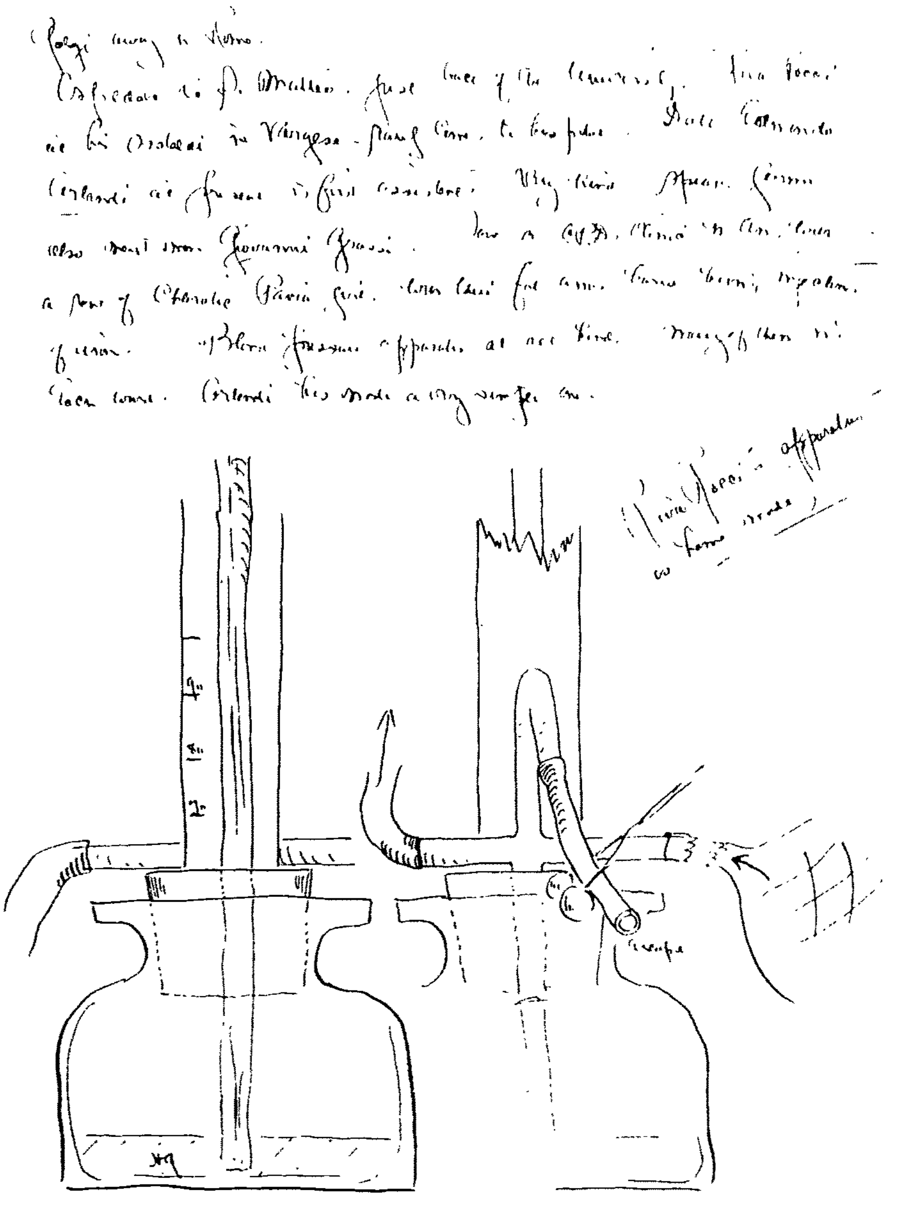


Figure 3. Sketch of Riva-Rocci's blood pressure apparatus from an entry in Cushing's diary dated May 6, 1901 (Yale Medical Library).

blood pressure appeared in September 1902 (10) and March 1903 (11). In the former article, Cushing presented data to show that cocaine applied to major nerve trunks could prevent the shock often associated with limb amputation. Cushing, therefore, shared similar views with George Crile, whose experiments had stimulated Cushing's work on the subject. On January 19, 1903, he presented a paper to a special meeting at the Boston Medical Library. The talk was titled "The Clinical Value of Blood Pressure Observation," and, as a result of this reading, the Harvard Medical School distributed a circular to all members of the Department of Surgery requesting that a committee be formed to consider the "importance of blood pressure determinations." After many meetings of this committee and a great deal of deliberation, it was eventually decided that "the skilled finger was of much greater value clinically for determination of the state of the circulation than any pneumatic instrument" (1,p214). Despite this decision, and possibly due, in part, to the publication of George Crile's monograph "Blood Pressure in Surgery" (12), clinicians throughout the country began to record blood pressure during surgical procedures. Cushing, therefore, must be given a great deal of credit for the introduction and acceptance of blood pressure determinations into America. An amusing anecdote from this period appears in Fulton's biography of Cushing (1,p216). During a

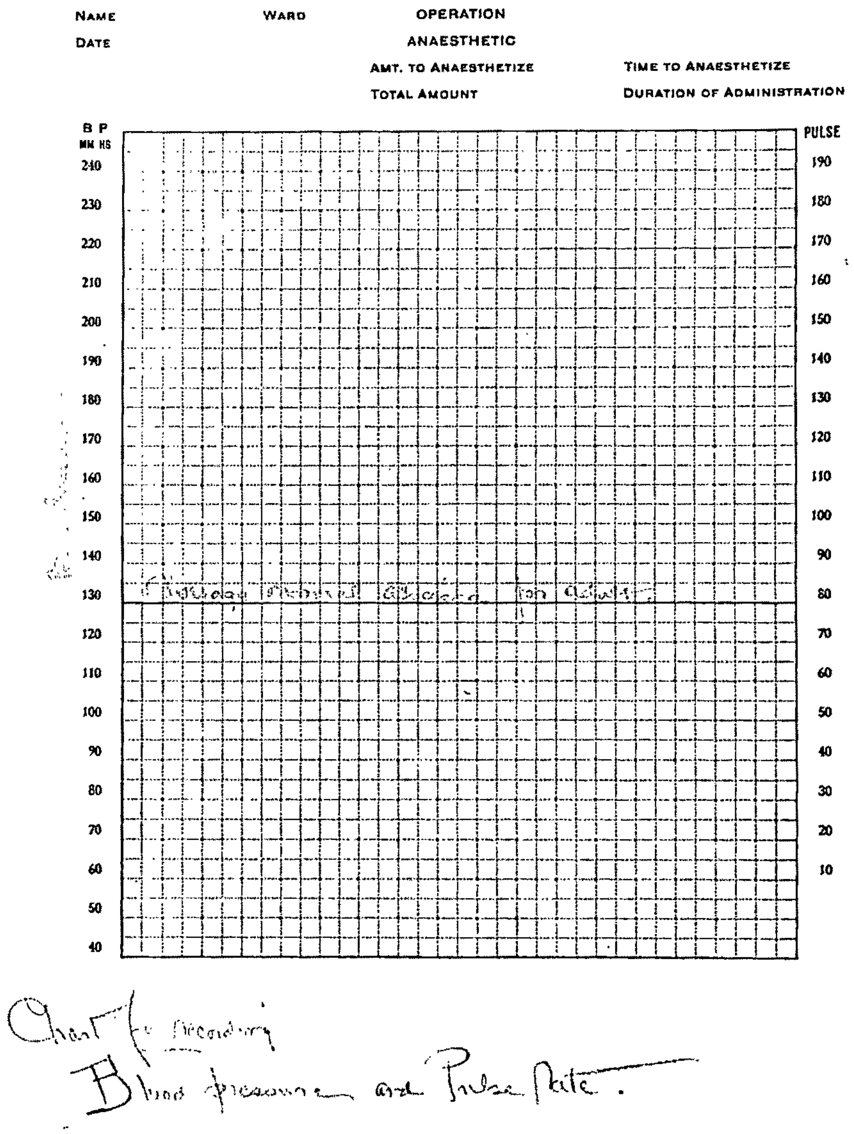

NAME
WARD
OPERATION
DATE
ANAESTHETIC
AMT. TO ANAESTHETIZE
TIME TO ANAESTHETIZE
TOTAL AMOUNT
DURATION OF ADMINISTRATION
B P MM HG
PULSE
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
Chart for Recording
Blood pressure and Pulse Rate.

Figure 4. Cushing's original blood pressure chart with comments by its designer. It was introduced into practice in 1902 (Yale Medical Library).

tense moment in an operation, an inexperienced student nurse, who was substituting as an anesthetist, was suddenly told to take a pressure reading. A few minutes later, Cushing felt something tugging at his trouser leg only to find that the nurse was putting the cuff on him!

Cushing's reservation concerning the administration of ether by medical students was still apparent at this time; this is illustrated by his adoption of a full-time physician anesthetist. Halsted believed that the administering of ether was an essential part of an intern's training, but Cushing felt that anesthesia by the "cone and struggle" method was inappropriate for neurosurgical operations. He therefore employed the services of Dr. S. Griffith Davis to administer anesthesia for him. Private patients paid for the service; for public patients Cushing paid Davis out of his own pocket (13). This is one of the first recorded instances in America of a surgeon employing another physician exclusively for the provision of anesthesia.

In 1912, Harvery Cushing was appointed Surgeon-in-Chief to the newly opened Peter Bent Brigham Hospital in Boston and as Professor of Surgery at Harvard. He continued to employ the services of a regular anesthetist, Dr. Walter Boothby. Boothby was replaced in 1916 by Gertrude Gerrard, the first nurse anesthetist at that hospital. In May 1917, Harvey Cushing was Surgeon-in-Chief of the American Expeditionary Base Hospital Number 5 in Boulogne, with Gerrard as anesthetist. She was also a member of his surgical team at an advance hospital in Belgium and, for her services there, she was decorated with the British Royal Red Cross.

On Cushing's return to private practice at Harvard, he continued to excel in the practice of neurosurgery, performing over 2000 craniotomies. On November 5, 1932, he performed his last operation—the removal of a highly vascular meningioma from a physician's daughter—and shortly after retired from Harvard. In 1933 he accepted the nonclinical post of Sterling Professor of Neurology at Yale, a position that he occupied until his death on October 7, 1939.

Harvey Williams Cushing will always be remembered for his pioneering work in the field of neurosurgery, but his contribution to the early days of anesthesia should not be forgotten.

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Review Article

An Appreciation of the Coronary Circulation

Dhun H. Sethna, MD, and Emerson A. Moffitt, MD

Management of patients with coronary artery disease, including those with previous myocardial infarctions, is an integral aspect of most anesthetic practices. Anesthesiologists who are not involved in anesthesia for cardiac surgery must occasionally handle coronary patients having other surgical interventions. A working understanding of the coronary circulation is hence necessary.

This review presents information, not related to anesthesia, in order to provide an appreciation of the coronary circulation. A succeeding article, to be published in next month's *Anesthesia and Analgesia*, relates the effects of anesthesia and anesthetic drugs on the coronary circulation and myocardial oxygenation in patients with coronary artery disease.

Anatomy

The human coronary arteries are conduit and capacitance vessels that usually deliver 90–180 ml/min of blood to the myocardium at a mean pressure of 90 mm Hg. The arteries arise from the aortic root, and subdivide into branches that run epicardially over the heart surface. The intramural blood supply, particularly of the thick-walled left ventricle, is provided by branches that supply the outer one-third of the myocardium, and by vessels that arise at right angles from these epicardial arteries and penetrate directly through the myocardium to form a subendocardial plexus (23). The total blood volume in all left ventricular coronary vessels is estimated at 6–15 ml/100 g left ventricular mass, of which less than 5% is present in epicardial arteries and veins (62).

Anatomical variation of the coronary arteries among species may account for differences in results of experimental studies. In humans, as in swine, rats, and nonhuman primates, the left anterior descending artery and its diagonal branches usually supply a larger mass of myocardium than the circumflex (17). In dogs, however, the circumflex artery supplies the largest mass of cardiac muscle (67). The first septal perforator artery in dogs lies very proximally, and supplies 12% of the left ventricular mass. Thus cannulation of the left main coronary artery in dogs during experiments has a higher potential of occluding the orifice of this vessel with resultant septal ischemia (67).

In humans, the coronary sinus, which empties into the right atrium, receives blood from 96% of veins from the left ventricular free wall and septum (38). However, 17% of its venous drainage arises from other structures. In 0.2% of normal subjects, and in 2% of patients with atrial septal defects, an anomalous left superior vena cava connects with the coronary sinus (26). Veins from the inferior or posterior left ventricle may empty separately into the right atrium, or may enter the last 2 cm of the coronary sinus where admixture with blood reflux from the right atrium can occur. In dogs, prominent interconnections are present between large coronary veins, so that blood draining from any specific vein does not contain effluent that arises exclusively from the apparent drainage field of the vessel (31).

The coronary arteries receive innervation through bilateral vagal (parasympathetic) fibers from the cardiac plexus at the base of the aorta and sympathetic nerves that, for vessels of the left ventricle, arise from the left stellate ganglion (19). Abundant afferent nerve fibers travel with the sympathetic and parasympathetic nerves (12). In anesthetized dogs, intravascular infusion of norepinephrine or electrical stimulation of sympathetic nerves can increase the resistance of large

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coronary arteries by an average of 60%; small vessels, however, respond mainly to the increased metabolism of surrounding myocardium (40). The physiologic role of vagal innervation remains unclear—presynaptic inhibition of release of norepinephrine from adrenergic nerve terminals by parasympathetic nerves may contribute to coronary vasodilation (46).

Measurement of Coronary Blood Flow in Humans

Because coronary flow varies within the left ventricle, flow measurement techniques must be able to take into account the wide distribution of local flows inevitably included in whatever single value is determined by the technique.

Mean steady-state left ventricular blood flow ("coronary blood flow") has been estimated in anesthetized patients by thermodilution or argon clearance. Thermodilution involves infusion of crystalloid at room temperature at an adequate rate (40 ml/min) for a limited time (20–40 sec) through an insulated catheter (25). The catheter is introduced into the right atrium percutaneously through the right internal jugular vein, and then directed, with fluoroscopy, into the coronary sinus. Hence it is the coronary venous (coronary sinus) blood flow that is measured. Coronary arterial and venous flows are assumed equal and constant during measurement times. The extent of left ventricular perfusion represented in the measurement is the portion of myocardial drainage entering the coronary venous system upstream to the flow measurement catheter. Results may be influenced by catheter position, arrhythmias, intrapleural pressure changes, reflux of right atrial blood into the coronary sinus, catheter displacement, and factors that may alter the temperature of coronary sinus blood (e.g., alterations in cardiac work, or pharmacologic vasodilation) (52,75,78). The frequency response of the system is rapid (2–3 sec), allowing flow changes to be detected at short time intervals. Excellent correlations exist between thermodilution flow and actual flow (timed venous collection) in animals with normal coronary arteries (25).

Argon is an inert gas with minimal blood solubility and virtually no recirculation and is completely eliminated in one passage through the lung (41,66). The inhaled gas is transported through the pulmonary venous blood to the arterial circulation. Arterial and coronary sinus blood argon concentrations are measured simultaneously by gas chromatography using radial artery and coronary sinus cannulation. The integrated difference between arterial and coronary sinus blood is proportional to coronary flow per unit tissue weight. It is assumed that coronary arterial and venous flows are constant and equal during measurement times (which can take up to 20 min), that the myocardium is homogeneously perfused, that tissue concentration of argon equals venous (coronary sinus) concentration, and that limitation of wash-in and wash-out of argon from vessel to tissue is flow, not diffusion. The method has been validated for coronary blood flow rates of less than 200 $\text{ml}\cdot\text{min}^{-1}\cdot 100^{-1}$ g (43,64). Compared to thermodilution, the frequency response of the system is slow (5–30 min). The argon method measures flow per unit mass but can yield absolute flows if ventricular mass is measured by echocardiography or angiography. Results are less accurate with nonhomogeneous than with homogeneous myocardial flows.

A limitation of both techniques is that a regional disease (coronary artery disease) is being evaluated by a global method (coronary sinus blood flow). Comparison of thermodilution values for flow with values of flow per unit weight are difficult without knowledge of left ventricular mass. Both methods estimate average steady-state flow only for the left ventricle and do not record phasic patterns of myocardial perfusion. Positron emission tomography and computerized x-ray tomography may allow more precise estimates of transmural myocardial perfusion in humans (68,76).

Phasic Coronary Blood Flow

Epicardial Arteries

The heart is unique among organs in that cardiac contraction that propels blood to the arteries also impedes perfusion of the myocardium. Cardiac contraction tends to reduce myocardial flow during systole, so that under normal conditions, 70–85% of coronary flow occurs during diastole (30). This phasic character of coronary blood flow can be examined in epicardial arteries by electromagnetic or ultrasonic flow meters. Because flow meters are applied to epicardial coronary arteries, they reflect flow patterns predominantly in these extramural vessels. Flow in the left coronary artery decreases abruptly at the onset of isovolumetric contraction and then later increases somewhat in systole (Fig. 1). Flow increases markedly during isovolumetric relaxation, peaks early in diastole, and then decreases slowly along with the decline in aortic pressure until the onset of the next systole. Thus phasic myocardial perfusion results from its dependence on phasic aortic pressure, and from compression of intramural coronary vessels by contracting myocardium. In dogs, right ventricular and

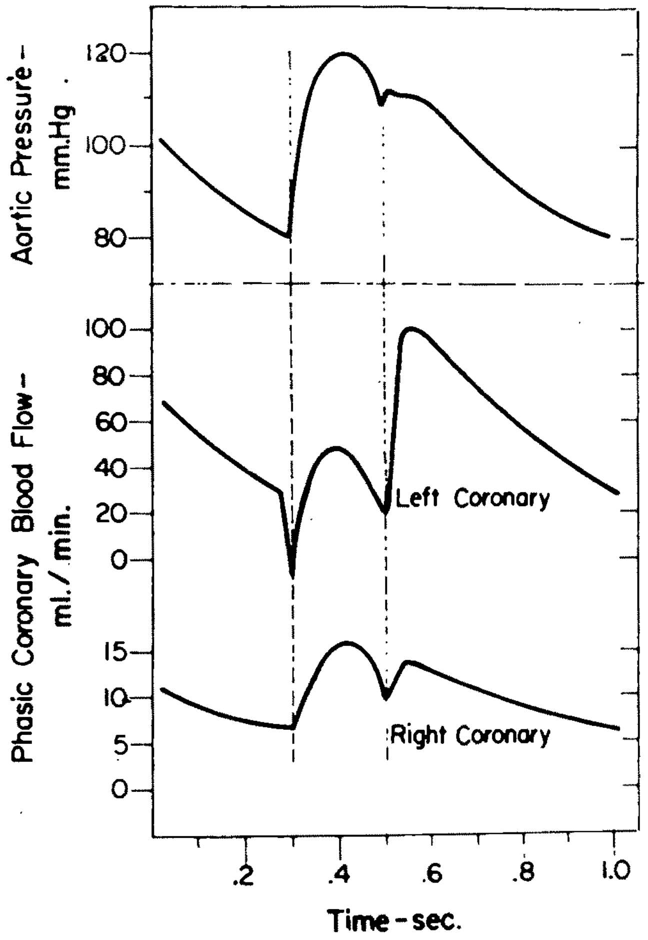

Figure 1. Comparison of phasic coronary blood flow in the left and right coronary arteries in relation to aortic blood pressure. (Reproduced by permission from R. M. Berne and M. D. Levy, Cardiovascular Physiology, 2nd ed. St. Louis: Mosby, 1972.)

atrial compressive forces are lower, and phasic flow in intramural right ventricular and atrial vessels is dominant in systole, resembling the usual flow patterns observed in peripheral arteries (79). In humans, however, if the right coronary artery also supplies the inferior wall of the left ventricle, phasic flow patterns in this vessel may resemble that of the left coronary artery with dominant flow in diastole (11). When right ventricular pressures are increased due to disease, phasic patterns of right coronary flow parallel those observed in the left ventricle (49).

Intramural Arteries

Phasic flow patterns observed in epicardial vessels may not accurately reflect those in intramural coronary arteries. Blood flow in systole in intramyocardial vessels is decreased by more than half when compared to epicardial arteries, with mid-systolic flow usually being retrograde (15,16). Intramural diastolic flow exceeds epicardial flow by 20%. Differences in flow characteristics between intramyocardial and epicardial arteries have been shown to be exaggerated by tachycardia, coronary vasodilation, aortic regurgitation, and right ventricular hypertension (15).

Transmural Distribution of Myocardial Perfusion

Transmural distribution of myocardial perfusion has been examined in animals using labeled microsphere techniques. These studies indicate that, in most awake animals at rest, subendocardial perfusion in both ventricles exceeds subepicardial perfusion (subendocardial/subepicardial perfusion ratio: 1.1–1.4 : 1) (36). This may reflect a transmural heterogeneity of vascular tone or a greater density of subendocardial vasculature (3,49), or may result from the greater wall stress, oxygen consumption, and metabolic activity present in the subendocardium (3,34). Tomographic thallium 201 scintigrams and $^{14}NH_4$ distribution studies in humans, however, suggest that transmural blood flow in humans may be more homogeneous (68,76).

Systolic Phase of Transmural Flow

When only the systolic phase of transmural flow is examined by the myocardial uptake of radioactive ions such as ^{86}Rb that are introduced into the coronary circulation, it is found that flow in subepicardial layers of the left ventricle is approximately twice that in the subendocardium (30). Some perfusion is always present in all layers of the myocardium in systole. This transmural flow gradient reflects a transmural intramyocardial pressure gradient during systole, which can be measured by small intramyocardial balloons or pressure sensitive needles (1,73). Systolic extravascular forces compressing intramural coronary arteries have a dual origin: physical compression, and shearing forces resulting from myocardial shortening that cause twisting of vascular channels as the heart contracts (21). Shearing forces are believed to be distributed evenly across the ventricular wall. Thus to explain the transmural flow gradient, physical compression must be greater in the subendocardium during systole. Most measurement techniques have found subendocardial intramyocardial systolic pressures to equal or exceed left ventricular cavitary pressures, whereas subepicardial pressures are below simultaneously measured aortic pressures (9,15). Under basal conditions, total extravascular compression accounts for about 10–25% of the resistance to coronary flow (21,72).

The contribution of systolic contraction to overall coronary resistance is not significantly altered after administration of isoproterenol, norepinephrine, or epinephrine—when the effects of these agents on heart rate are prevented (47). The impact of extravascular compressive forces is substantially magnified during coronary vasodilation (51) and may play an important role in modulating myocardial perfusion during ischemia when endogenous metabolites produce dilation of resistance vessels.

Diastolic Phase of Transmural Flow

Because coronary flow distribution during a cardiac cycle is uniform or slightly greater in the subendocardium than in the subepicardium under normal conditions, the reduced systolic subendocardial flow must be compensated for by an increase in subendocardial flow during diastole. Blood flow in diastole is normally controlled by the vasomotor activity of coronary resistance vessels, and intramyocardial pressures normally appear to have little effect on diastolic transmural distribution of myocardial blood flow. Under conditions of reduced coronary perfusion pressures or low pressures distal to an area of coronary stenosis, however, diastolic intramyocardial pressures may assume importance in determining the quantity and distribution of myocardial blood flow.

Flow is predominantly to the subendocardium during diastole. The ability of the heart to augment subendocardial blood flow during diastole may be related to active coronary vasodilation and to an anatomic gradient of vascularity that exists across the left ventricular wall, with greater vascular density in the subendocardium than in the subepicardium (2,20,81). During maximal coronary vasodilation at normal heart rates, the anatomic gradient of vascular density favoring blood flow to the subendocardium during diastole appears adequate to compensate for the underperfusion of the subendocardium that occurs during systole (2,20,81). However, active coronary vasomotion is required to adjust the relative subendocardial/subepicardial resistances in order to compensate for alterations in diastolic and systolic time intervals that occur with increased or changing heart rates. With intact coronary vasomotor tone, pacing has been shown to increase mean myocardial blood flow in response to increasing myocardial oxygen consumption, despite the relative increase in time spent in systole with increasing heart rates; and overall transmural myocardial perfusion remained uniform at all pacing rates (28). These observations suggest that vasomotor adjustments not only increase mean myocardial blood flow to meet increasing metabolic demands during increasing heart rates, but also that autoregulation, the process by which resistance vessels adjust coronary blood flow over a wide range of perfusion pressures, additionally adjusts diastolic subendocardial resistance relative to subepicardial resistance in order to compensate for the decreasing time in diastole available for subendocardial perfusion. When active coronary vasomotion is abolished by administration of adenosine, increasing pacing rates are associated with progressive decreases in subendocardial blood flow in proportion to rate-dependent decreases in the diastolic interval, confirming the importance of local vasomotor activity in maintaining uniform transmural myocardial perfusion during changes in heart rate.

The DPTI/SPTI Ratio

An index described to predict transmural distribution of myocardial perfusion is the DPTI/SPTI ratio (DPTI being the diastolic pressure time index and SPTI the systolic pressure time index) (36,37). Conceptually, SPTI relates to the myocardial oxygen demand, and DPTI reflects myocardial oxygen supply (coronary blood flow), which is delivered primarily during diastole. Labeled microsphere studies in anesthetized dogs demonstrate a linear relation between DPTI/SPTI ratios of less than 0.8 and measured subendocardial/subepicardial flow ratios over a wide range of hemodynamic interventions (37). This index, however, is useful only after maximal vasodilation has occurred, and coronary reserve is exhausted. Recent studies indicate that drugs, neural stimuli, and cardiac hypertrophy alter transmural perfusion before coronary reserve is exhausted, thus limiting the utility of this index (79). Further, the index does not account for effects of inertial factors confined mainly to larger arteries where velocities are significant, coronary capacitance effects related to vessel elasticity, and blood viscosity (37,79).

Hemodynamics of Coronary Blood Flow

The physical factors that determine laminar flow of Newtonian fluids through rigid tubes are expressed in the Poiseuille equation:

$$\text{Laminar flow} = \frac{\Delta P \, \pi r^4}{8 \, L\eta}$$

where ΔP = pressure gradient, r = radius of tube, L = length of tube, and η = fluid viscosity. The Poiseuille relationship provides a convenient expression of hemodynamic concepts in clinical practice, even though blood, because of the cells present in the plasma, is a non-Newtonian fluid flowing through compliant blood vessels in which flow is frequently turbulent. In the coronary arteries, the length of the vessel and, under normal conditions, blood viscosity are constant, so that the primary physical factor controlling coronary blood flow is the fourth power of the radius of coronary resistance vessels.

Klocke has conveniently described total coronary resistance as the sum of three time-dependent functional components in the subendocardium and subepicardium, with each component playing a varying role during systole and diastole (41). The components are categorized as follows: basal viscous resistance, which is the impedance to flow offered by the entire coronary bed during diastole when fully dilated—it is the minimal possible resistance; autoregulatory resistance, which is due to tonic contraction of vascular smooth muscle—it is normally the major component of resistance; compressive resistance, which represents the increase in resistance due to compression of intramural coronary vessels by intramyocardial pressure—it is of importance during systole. Viscous resistance is therefore a relatively static factor on which the more dynamic autoregulatory and compressive resistances are superimposed.

Whereas accurate measurements of coronary vascular resistance can be obtained in studies measuring phasic and transmural coronary blood flow, the validity of calculated values may be less certain in patients when based on measurements of mean coronary blood flow. Such calculations, although frequently used, disregard the potential contributions of extravascular compressive forces, coronary capacitance, and tissue back-pressure.

Coronary Flow Reserve

Coronary pressure–flow relations have been studied in perfused hearts in which coronary perfusion pressure can be varied, while left ventricular work and oxygen consumption are kept stable (53). Under these conditions, rapid alterations in coronary vascular resistance maintain a constant blood flow over a wide range of perfusion pressures (60–130 mm Hg) (Fig. 2). Coronary autoregulation (the process by which resistance vessels adjust coronary blood flow to fluctuating metabolic activity of local myocardium) is more effective in the subepicardium; the autoregulatory capacity of the subendocardium is exhausted before that of the subepicardium (8,79). Myogenic, neurohumoral, and metabolic mechanisms for autoregulation have been described; adenosine, and possibly carbon dioxide, currently are regarded as important metabolites controlling autoregulation (7).

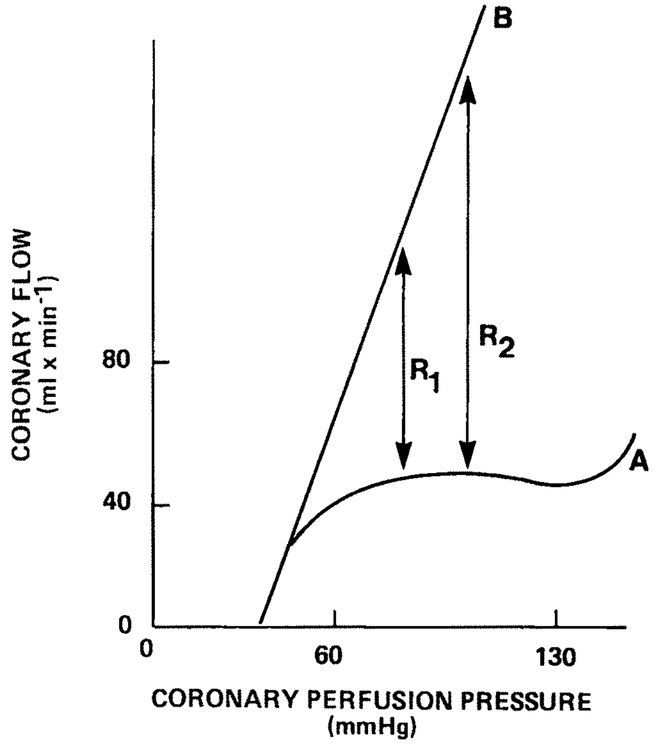

Figure 2. Graphic representation of coronary pressure–flow relationships in normal left ventricle showing baseline (autoregulatory) flow (A) and maximal vasodilation (B) to illustrate the concept of coronary reserve. R_1 and R_2 represent coronary flow reserves at two mean coronary perfusion pressures. Maximal vasodilation may be produced by infusion of vasodilators like adenosine, ATP, or dipyridamole, or by producing a maximal reactive hyperemic response to a 20-sec occlusion of a coronary artery. (See references 7,35,50.)

It has been shown with the same experimental models that the pressure–flow relationship during maximal coronary vasodilation is approximately linear (35) (Fig. 2). The difference between mean basal coronary flow and maximal coronary flow constitutes a coronary vascular flow reserve that can be called upon to satisfy accelerating flow demands, and is approximately sixfold in humans and experimental animals. Coronary reserve indicates the total cross-sectional area of the coronary resistance vessels and what might happen during maximum stress, provided that interfering factors such as heart rate, contractility, end-diastolic pressure, and blood viscosity are held constant. The value is also critically dependent on perfusion pressure. Coronary reserve is reduced by polycythemia, coronary artery disease, pressure or volume overload hypertrophy, increased contractility, tachycardia, and large increases in left ventricular diastolic pressure (35). Conversely, a decrease in contractility may increase maximal flows and decrease resting flows, thereby increasing coronary reserve.

Coronary flow reserve cannot be represented by a single value because of its dependence on perfusion pressure, and ideally should be measured at different perfusion pressures. However, because it is difficult to examine coronary flow in patients during autoregulation and maximal vasodilation over a range of perfusing pressures, reported studies have used only one perfusion pressure. Estimation of coronary flow reserve requires the ability to detect rapid, transient changes in flow. This can be achieved by catheter tip ultrasonic velocity meters placed in a coronary artery, or ultrasonic velocity meters placed on a coronary artery at surgery (35,50). Results have been expressed as the absolute or the relative coronary flow reserve (maximal flow divided by resting flow).

When perfusion pressure is below the lower end of the autoregulatory range, flow becomes dependent on mechanical factors, including duration of diastole and the perfusion pressure. Subendocardial flow becomes inadequate for metabolic needs when diastole is severely compromised by reduced diastolic pressure or abbreviation of diastole.

Critical Closing Pressure: Zero-Flow Pressure

Recently investigators have related simultaneous coronary flow and perfusion pressure measurements obtained during prolonged diastoles (6,45). Repeated, simultaneous measurements during a single diastole permit construction of pressure–flow curves (Fig. 3), which show that myocardial perfusion virtually ceases when coronary artery pressures decrease below a critical value (called zero-flow pressure: P_{zf}). This absence of flow implies that coronary arterial pressure must be balanced with a back-pressure, most likely arising within the myocardium. Hence this analysis suggests that coronary pressure–flow relations must consider myocardial back-pressure as well as coronary vascular resistance. Myocardial back-pressure represents a summation of forces that tend to collapse microvessels: tissue pressure, vessel tone and elasticity, and surface tension. Myocardial tissue pressure, in turn, reflects intracavitary pressures (particularly within subendocardial layers) and marked elevations of venous pressures.

When no antegrade flow is detected by a flowmeter over a proximal coronary artery, the pressure measured in a distal segment of the same artery is presumed to be the P_{zf}. If flow were present in the distal segment from collateral vessels or because of capacitance in the coronary arteries, the values assumed to represent zero-flow would be erroneously high. Dogs, which have an extensive collateral circulation, have P_{zf} values that are very high (up to 30 mm Hg), and well above coronary sinus or right atrial pressures (6,22,45). If the P_{zf} values in humans were as high, aortic mean diastolic pressures near this level would not provide sufficient driving pressures to maintain adequate coronary flow. In contrast, swine, which have a coronary circulation more comparable to that of humans, have P_{zf} values of 7–12 mm Hg, which are close to right atrial pressures (59). This low P_{zf} is beneficial in maintaining flow at lower coronary artery perfusion pressures. In addition, increases in heart rate, short-term elevations in left ventricular and coronary arterial systolic pressures, or autonomic blockade, appear not to alter P_{zf} values in swine (59). Zero-flow pressures as currently described are based on measurements in epicardial arteries and may not reflect pressure–flow relations within the myocardium.

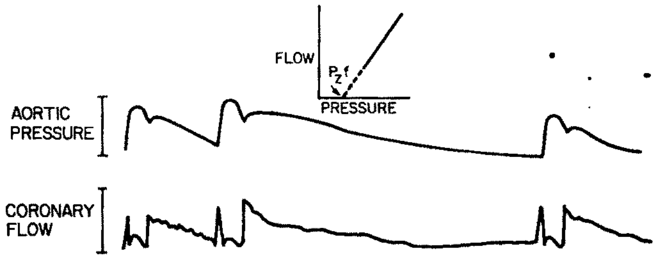

Figure 3. Graphic representation of coronary pressure–flow relationships during a single, long diastole. Long diastoles are achieved by the arrest of pacing in animals with atrioventricular block, or by vagally induced sinus node arrest. Coronary flow is recorded with a flowmeter placed on an epicardial artery, and pressure is measured simultaneously in the same artery (or in the aortic root). The inset shows a graphic plot of simultaneous pressure and flow measurements obtained during the long diastole (solid line). Linear extrapolation of this relation to the abscissa indicates the pressure at which flow through the artery is zero (zero-flow pressure: P_{zf}). The slope of the line is the reciprocal of coronary vascular resistance. The value of P_{zf} would alter with changes in slope (see references 6,44,45,59).

The clinical significance of P_{zf} lies in calculations of coronary vascular resistance. If the effective back-pressure to coronary flow is not coronary venous (coronary sinus) pressure, but rather P_{zf}, then coronary driving pressure would equal mean aortic pressure minus zero-flow pressure, instead of mean aortic pressure minus coronary sinus pressure. Most reported values of coronary resistance may need to be reconsidered because of a probable overestimate of coronary driving pressure, even when measured flows were methodologically secure. Although investigations have supported the concept that coronary flow is influenced by a back-pressure that exceeds coronary venous pressure, left ventricular diastolic pressure, or both, there has been concern that this finding may be a methodologic peculiarity of the experimental approaches (44) to study it.

Regulation of Coronary Blood Flow

Metabolic Factors

Myocardial oxygen consumption is the primary determinant of coronary blood flow. A linear relation exists between global and regional left ventricular flow and left ventricular oxygen consumption over a wide range of coronary flow rates in all species studied, and this coupling is a dynamic one that is continuously being adjusted. Increases in myocardial oxygen demand in one cardiac cycle can result in reductions in coronary vascular resistance and increases in coronary blood flow in the following cycle (70). Because of the quantitative coupling of coronary flow to myocardial oxygen demand, the interpretation of any specific value for flow as "normal" or "abnormal" requires an ability to relate the value of flow to some index of myocardial metabolic demand at the time of measurement.

The major determinants of myocardial oxygen consumption are heart rate, myocardial wall stress, and contractility (10). Under basal conditions, the myocardial oxygen consumption rate is 8–10 ml·100 g^{-1}·min^{-1} (about 70% oxygen extraction) leaving coronary sinus blood about 30% saturated at $Po_2$18–20 mm Hg. Even when arrested, the heart consumes considerably more oxygen (1–2 ml·100 g^{-1}·min^{-1}) than resting skeletal muscle (0.1–1.2 ml·100 g^{-1}·min^{-1}). In most situations increases in oxygen demand are met by augmentation of coronary blood flow, with coronary sinus oxygen saturation remaining remarkably constant.

Neural Factors

The effects of neural stimulation as an independent factor altering coronary blood flow in the presence of concomitant vasodilatory metabolic stimulation have been recently examined (13,54,57,61,71,74). It is well known that occlusion of a major coronary artery for several seconds results in marked coronary vasodilation (reactive hyperemia) due to accumulation of vasoactive metabolites. Removal of the left stellate ganglion in dogs, however, substantially increases the hyperemic response to a 10-sec occlusion (71). Similar responses occur after α-adrenergic blockade with phentolamine, thus demonstrating the ability of sympathetic vasoconstrictor tone to compete with metabolic coronary vasodilation. On a similar theme, studies in chronically instrumented dogs during maximal exercise showed that α-adrenergic blockade increases coronary flow to a greater extent than could be explained by increases in myocardial oxygen demand, suggesting that coronary reserve is not exhausted at peak exercise, and that α-adrenergic vasoconstriction could effectively compete with increases in metabolic vasodilation during exercise (54). The heart does not contribute to the increase in plasma norepinephrine levels observed during severe exercise, but may actually take up norepinephrine, implying increased cardiac efferent fiber activity, reuptake, receptor binding, and catecholamine metabolism during exercise (61). In another study, sympathetic coronary vasoconstriction could still be demonstrated in the presence of coronary stenosis, implying that the vasoconstrictor response was not abolished by limited coronary flow (13). The overall evidence appears to indicate that vasoconstrictor tone can restrict coronary flow by up to 30% in the presence of potent metabolic vasodilation (74).

Coronary vessels have sympathetic adrenergic and muscurinic cholinergic receptors; their density in different segments of the coronary vasculature, however, remains ill-defined. Increases in coronary vascular resistance with stellate ganglion stimulation after β-blockade, but not after α-blockade or prior catecholamine depletion with reserpine, indicate the presence and function of coronary α-adrenergic receptors (7). Dilation by isoproterenol of the coronary vascular bed in potassium-arrested hearts without concomitant changes in MVo_2 suggests the presence of coronary β_2-adrenergic receptors. The physiologic significance of α_2- and β_1-receptors in coronary vessels is not clear (30). There is no evidence for sympathetic cholinergic innervation of the coronary arteries (7). Vagal stimulation can elicit coronary vasodilation, but the effect is not great and is probably not of much physiologic significance (7).

Coronary Collateral Circulation

Collaterals are thin-walled anastomotic connections that exist between coronary arteries without an intervening capillary bed. They are anatomically present from early life, but enlarge only if the need for additional coronary flow exists in some region of the heart. Collateral vessels may occur in series, from the proximal to the distal portion of the same coronary artery, or in parallel, from one coronary artery to the postocclusion segment of another artery.

Transformation of native collateral channels, in response to an ischemic stimulus or a pressure gradient between normal and occluded arteries, consists of an initial rapid increase in luminal diameter to quickly meet increased demands for blood flow, followed by a more gradual architectural remodeling of the enlarged collateral vessel to ultimately resemble a normal artery (65). The sudden initial widening of native collateral vessels results in increased wall stress with edema and breakage of the vessel wall. This is accompanied by DNA replication with reparative mitotic activity observed in fibroblasts, endothelial cells, and smooth muscle cells. After 1–2 weeks, the vessel becomes a larger (up to an eightfold luminal increase), thicker-walled channel, and reaches near maximal functional capacity within 4 weeks. Six to 12 months after coronary occlusion, collateral vessels may resemble normal coronary arteries of similar size. Collaterals regress when coronary circulation is restored.

In dogs, collateral flow after acute coronary occlusion ranges between 8–36% of normal coronary flow (65). With gradual, severe (90%) stenosis, well-developed collateral flow in dogs may equal normal coronary blood flow, suggesting that resistance through collateral beds need not be excessive. Native collaterals generally show modest responsiveness to vasodilators and other drugs (15,28). The influence of vasodilators is more consistent and pronounced in collaterals from hearts with chronic occlusive lesions (15,28).

Coronary Steal

Proximal stenosis of a coronary artery usually results in compensatory reductions of distal vascular resistance (vasodilation) in an attempt to maintain normal coronary blood flow (42,56). In addition, perfusion to a potentially ischemic distal bed can occur via collaterals arising from an adjacent channel. Any stimulus for coronary arteriolar vasodilation will increase flow in normally perfused areas that are capable of undergoing vasodilation ("nonischemic bed"), but will have little effect in collateral-dependent areas where arteriolar dilation is already present ("ischemic bed") (Fig. 4). Dilation of the nonischemic bed (Fig. 4) can result in diversion of blood flow from R_1 by collateral vessels ("coronary steal") if, and only if, R_2 is flow-limiting. If perfusion pressure is maintained at the origin of collaterals, regardless of the magnitude of flow delivery, no steal is possible. Thus a necessary condition for steal is excessive resistance or a stenotic branch proximal to the origin of collateral vessels resulting in a decrease in local perfusion pressure, thereby decreasing perfusion pressure available at the takeoff of the collateral channels (5). Because of the well-known dependency of coronary collateral flow on perfusion pressure, this reduction of pressure would be expected to reduce collateral perfusion and, perhaps, reverse it (R_1 to R_2 in Fig. 4). Although it has been proposed that a pressure decrease sufficient to cause coronary steal during arteriolar vasodilation requires a proximal stenotic lesion in the artery supplying the collateral channels, investigators have demonstrated that if sufficiently intense arteriolar vasodilation is produced, collateral flow may decrease even in the absence of such proximal stenoses (15,60).

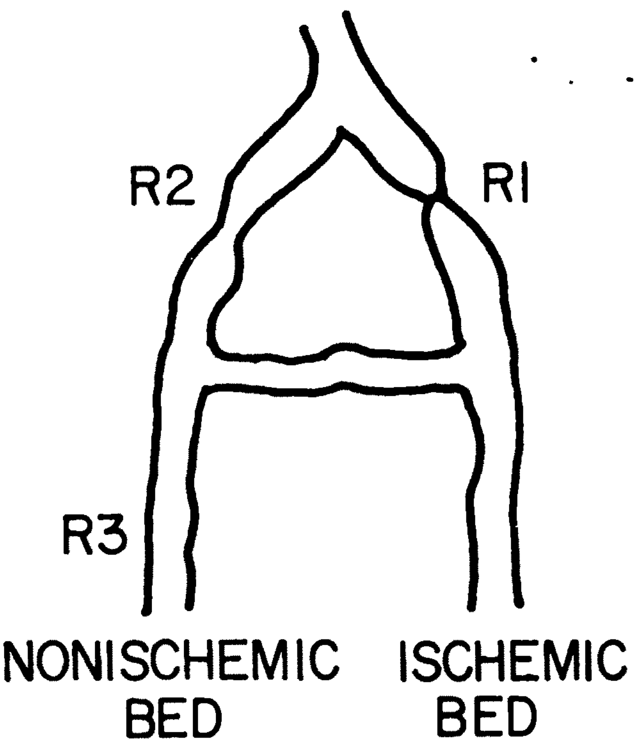

Figure 4. Diagrammatic representation of the phenomenon of coronary steal. Dilation of the "nonischemic" bed can result in diversion of flow from R_1 by collaterals only if R_2 is flow-limiting; e.g., mild proximal stenosis. Because collateral flow is pressure-dependent, reduction of pressure at R_2 would reduce collateral perfusion and, eventually, could reverse flow (R_1 to R_2: coronary steal). Coronary steal will not be possible if a significant obstruction is present at R_3 (see references 5,15,29).

It has also been proposed that in order for coronary steal to occur the intercoronary collateral system must be poorly developed so that resistance to flow resides within the collateral channels, thereby requiring maximal or near maximal vasodilation of arterioles in collateral-dependent myocardium during basal conditions (15,39). If a well-developed collateral system in which the collateral vessels have characteristics resembling normal arteries is present, then the major resistance to blood flow is not in the collateral channels but at the level of the arterioles within the collateralized myocardium, so that coronary steal would be much less likely to occur in response to arteriolar vasodilation (39).

Substantial experimental data support the concept of coronary steal. Studies of regional myocardial blood flow in animals with occlusion of a major coronary artery have demonstrated that vasodilators that act principally at the arteriolar level, including isoproterenol, dipyridimole, adenosine, and nitroprusside, markedly increase blood flow in normally perfused areas of the myocardium, but have the potential for decreasing flow in collateral-dependent areas (14,18, 24,80). In contrast, an agent like nitroglycerin, with potent dilator influence on collateral channels, might produce a balanced increase in flow or might direct flow selectively towards potentially ischemic regions (29). Hence coronary vasodilator properties do not necessarily imply an ability to augment coronary perfusion in a useful manner.

Extrapolation of findings in experimental animals to humans is complicated by important differences among species in collateral circulation and by an inability to model human coronary artery disease adequately (79). In dogs, collateral vessels are normally well-developed and located in the epicardium. In swine, few collaterals can be demonstrated, and sheep have none. It has been proposed that because swine have minimal collateral circulation, as do humans without chronic coronary artery disease, they may be appropriate animals to study normal coronary physiology or the development of collateral circulation. In contrast, results from studies in dogs might be more applicable to humans with chronic coronary artery disease wherein variable, yet in many cases substantial, coronary collateral flow exists.

Coronary Stenosis

Proximal coronary stenosis with reductions in arterial diameter up to 80% results in compensatory vasodilation of the distal coronary vasculature in an attempt to maintain normal coronary blood flow, with the capacity for additional vasodilation ("coronary reserve") being forfeited. The degree of coronary artery stenosis that elicits maximal distal vasodilation has been termed "critical" coronary stenosis, indicating that further reduction in luminal area will result in decreased coronary blood flow. Pressure–flow measurements across a proximal coronary stenosis show a nonlinear relation between stenosis resistance and degree of stenosis, with resistance at any given flow increasing substantially when stenoses exceed 50% internal diameter. An important change in clinical status can result from a small increase in severity of an established stenosis; conversely, a small decrease in stenosis severity, either static or dynamic, could have therapeutic benefit. Flow across coronary stenoses is further influenced in an unpredictable way by the length of the stenosis, occurrence of discrete obstructions in series, and loss of kinetic energy by turbulence at the exit of a stenosis.

Reductions in coronary flow to an extent that flow is insufficient to meet myocardial metabolic needs are accompanied by redistribution of transmural myocardial perfusion, with preferential delivery of the limited blood supply to the subepicardium, so that biochemical indicators of ischemia are initially detected in the subendocardium (32). Whereas only 10–15% of total coronary inflow occurs in systole during normal resting conditions, this fraction typically increases to 30–40% of total inflow in the presence of a proximal coronary stenosis (4). Several mechanisms may contribute to this redistribution of myocardial blood flow (15,63). It has been proposed that in the presence of marked reductions in diastolic perfusion pressure that may occur distal to a coronary stenosis, diastolic intramyocardial tissue pressures, which are greater in the subendocardium than the subepicardium, may act to impede diastolic subendocardial blood flow. Further, maximal distal coronary vasodilation (no coronary reserve) results in loss of ability of the coronary microvasculature to produce dynamic adjustments of subendocardial vascular resistance relative to subepicardial resistance, particularly when diastole is abbreviated by changes in heart rate (2).

Metabolic Indices of Myocardial Ischemia

Cardiac muscle has a versatile appetite, with adenosine triphosphate (ATP) being generated from many available substrates (glucose, fatty acids, ketone bodies, lactate, pyruvate, and amino acids) (33,55,48). The heart utilizes whichever substrate is presented to it in the highest concentration. Fatty acids are oxidized in preference to carbohydrates and usually account for 60–70% of oxidative metabolism. With ischemia, oxidative phosphorylation decreases as use of fatty acids is inhibited. Glucose transport increases and anaerobic glycolysis now predominates as the source of ATP production. Glycogen stores are depleted rapidly; with prolonged ischemia, the rate of ATP production by glycolysis is insufficient to maintain normal tissue levels of creatine phosphate and ATP. Irreversible myocardial changes, manifested as a depleted adenine nucleotide pool and structural mitochondrial changes, generally occur after 40–60 min of complete ischemia.

Under normal, aerobic conditions, the healthy heart consumes lactate, converting it to pyruvate as a substrate for mitochondrial oxidative metabolism. However, ischemia inhibits oxidative metabolism and, thus, less lactate is converted to pyruvate. Compounding the inhibition of lactate utilization is ischemia-induced transient stimulation of anaerobic glycolysis and, consequently, pyruvate production. The reduced capacity for pyruvate oxidation leads to its accumulation and conversion to lactate that accumulates in and leaks from the cell. Thus early ischemic damage may be characterized by a transition from lactate uptake to lactate production (69,77).

Lactate, with H^+, K^+, PO_4, inosine, and hypoxanthine can predictably be found to leak from ischemic myocardium, and can be sampled from the coronary vein draining the ischemic area (58). Sampling at the coronary sinus, however, causes dilution of these metabolites because of the much larger volume of blood draining nonischemic muscle, resulting in a great loss of sensitivity and value. Ischemia in one portion of the heart may not be reflected by either sampling or flow measures in the coronary sinus.

The normal myocardium uses lactate in proportion to the arterial concentration. Investigators frequently report the percentage of lactate extraction, with less than 10% extraction constituting evidence of ischemia (77). It is desirable to measure lactate extraction rather than lactate uptake, because low arterial lactate levels will result in low coronary arteriovenous differences without necessarily indicating the presence of anaerobic metabolism. Recently, Gertz et al., using a tracer method, showed that myocardial lactate metabolism is heterogeneous at rest in patients with coronary artery disease—a significant amount of lactate can be released by the myocardium at a time when chemical arterial–coronary sinus analysis indicates global extraction (27).

Summary

Coronary sinus catheter techniques for evaluation of coronary flow and myocardial metabolism have the drawback that a global sampling method is used to evaluate a regional disease (coronary artery disease). Studies on the coronary circulation are further limited by the fact that interventions acting on the coronary bed may simultaneously modify several of the principal determinants of coronary blood flow. Results are also influenced by differences among species, and whether the coronary vascular bed is normal or pathologically narrowed. Because coronary flow is intimately coupled to myocardial oxygen demand, interpretation of values as abnormal require simultaneous evaluation of some index of myocardial oxygen consumption.

Under normal conditions, myocardial flow is predominantly in diastole, and is subject to compromise by factors that abbreviate diastole (e.g., tachyarrhythmias). Autoregulation maintains constant coronary blood flow over a range of perfusion pressures (60–130 mm Hg), and increased flow demands are normally met by coronary vasodilation (coronary flow reserve). In proximal coronary stenosis, this capacity for additional vasodilation may be significantly reduced, and flow to potentially ischemic beds beyond the stenosis may be maintained by collaterals. Pharmacologic coronary vasodilation in this situation can result in coronary steal. When perfusion pressure decreases below the autoregulatory range, or when coronary flow reserve is exhausted early, as in coronary stenosis, flow becomes dependent on mechanical factors including duration of diastole and the perfusion pressure. In these situations, monitoring heart rate and diastolic pressure would allow reasonable assessment of adequacy of coronary flow and myocardial perfusion.

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Clinical Reports

Leukotrienes in Pulmonary Edema Fluid after Cardiopulmonary Bypass

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Leukotrienes are a class of potent mediators of hypersensitivity and inflammation generated by the 5-lipoxygenation of arachidonic acid and the further addition of polar substituents. Evidence for their role in producing and amplifying inflammatory responses in a variety of immunopathologic situations is accumulating, although clinical studies in humans are limited. The development of specific and sensitive radioimmunoassays has allowed detection of elevated concentrations of leukotrienes in several disease states including asthma (1), cystic fibrosis (2), neonatal hypoxemia with pulmonary hypertension (3), and, recently, the adult respiratory distress syndrome (ARDS)(4). The following case report describes an episode of pulmonary edema after cardiopulmonary bypass (CPB) that was associated with markedly elevated leukotriene levels in the edema fluid.

Case Report

A 67-year-old man with aortic stenosis, three-vessel coronary artery disease, and good left ventricular function, underwent aortic valve replacement and coronary artery bypass grafting with fentanyl, pancuronium, enflurane, and nitrous oxide anesthesia. Aortic cross clamp time was 68 min and nonpulsatile CPB time was 139 min (Cobe 4 roller head CPB machine). At the termination of CPB, protamine sulfate, 50 mg, was administered intravenously. There were no significant hemodynamic alterations throughout the operation. Shortly before leaving the operating room, the patient received two units of fresh frozen plasma in addition to three units of cell-saver blood.

Upon arrival in the intensive care unit (approximately 75 min after CPB), the patient's rectal temperature was 35.9°C, heart rate 67 beats/min (sinus rhythm), mean arterial pressure (MAP) 62 mm Hg, and central venous pressure 6 mm Hg (Table 1). A chest radiograph demonstrated a pattern consistent with diffuse pulmonary edema, and arterial blood gas tensions with an $\mathrm{FI_{O_2}}$ of 0.7 included a $\mathrm{P_{O_2}}$ of 53 mm Hg. Approximately one hr later, the MAP decreased to 40 mm Hg unassociated with a temperature change. The patient's hypotension was initially unresponsive to both aggressive volume administration—4 units of whole blood, 4 units of fresh frozen plasma, and 6 L of crystalloid—as well as vasopressors (calcium chloride, dopamine, and epinephrine). After 45 min the MAP increased to 60–65 mm Hg. A pulmonary artery catheter, which had been inserted after volume resuscitation, showed no significant elevation of right or left heart filling pressures but a high cardiac output of 6.7 L/min (by thermodilution). Calculated pulmonary vascular and systemic vascular resistances were both low (Table 1).

During this period of hypotension, the patient developed diffuse inspiratory and expiratory wheezes, and approximately 500 ml of frothy edema fluid was suctioned from the endotracheal tube. Samples of edema fluid were collected by suctioning with a soft plastic catheter, and a radial arterial blood sample was obtained concurrently. The edema fluid had a total protein content of 4.2 g/dl, which was 87% of the concentration in the plasma of the arterial sample. The albumin content of the edema fluid was 2.9 g/dl or 100% of the venous plasma albumin concentration.

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Table 1. Time Course of Adult Respiratory Distress Syndrome

	Day 1			Day 2
Time	1200	1300	1345	0800
F_{IO_2}	0.7	1.0	1.0	0.6
PEEP	5	12.5	12.5	10
P_{O_2}	53	36	45	100
MAP	62	40	65	75
CVP	6	8	10	15
PAP	—	—	21	25
PCWP	—	—	17	20
CO	—	—	6.7	4.8
SVR	—	—	657	1000
PVR	—	—	48	83

Abbreviations: PEEP, positive end-expiratory pressure (cm H_2O); MAP, mean arterial pressure (mm Hg); CVP, central venous pressure (mm Hg); PAP, mean pulmonary artery pressure (mm Hg); PCWP, pulmonary capillary wedge pressure (mm Hg); CO, cardiac output (L/min); SVR, systemic vascular resistance (dyne-sec/cm^5); PVR, pulmonary vascular resistance (dyne-sec/cm^5).

Both these values are consistent with a marked increase in alveolar–capillary permeability characteristic of ARDS (5). Edema fluid leukotriene D4 and B4 levels were determined by radioimmunoassay, as described previously, employing rabbit antisera of high specificity (4). D4 and B4 levels were markedly elevated at 43 and 10 pmol/ml, respectively.

The patient's clinical condition gradually improved over the next 24 hr with stabilization of hemodynamics and improvement in oxygenation. Over the subsequent 3 days the patient underwent a diuresis and was successfully extubated. He was discharged on the twelfth hospital day.

Discussion

Leukotrienes have been shown to possess properties consistent with a major role as mediators of inflammation (6). Cysteine-containing leukotrienes including D4 are potent bronchoconstrictors with preferential effects on peripheral airways in animals and in humans. Furthermore, they have been demonstrated to increase vascular permeability at much lower concentrations than histamine. Leukotriene B4 released from alveolar macrophages and other leukocytes serves as a potent chemotactic factor for blood neutrophils in vitro and in vivo and stimulates neutrophil adhesion to endothelial cells with subsequent degranulation, enzyme release, and superoxide generation (6).

Elevated levels of leukotriene D4 in pulmonary edema fluid in a group of ten patients with noncardiogenic pulmonary edema have recently been reported (4). In contrast, levels of leukotriene B4 were elevated in only five of these ten patients with ARDS. None of the patients in that study developed ARDS after cardiopulmonary bypass. In the present case, levels of both leukotriene D4 and B4 in pulmonary edema fluid were elevated at 43 and 10 pmol/ml, respectively, as contrasted with levels of leukotriene D4 and B4 of 4.4 ± 1.1 pmol/ml and 5.5 ± 2.8 pmol/ml (mean ± SD) in pulmonary edema fluid of patients with cardiogenic pulmonary edema (4). The high level of leukotriene D4 in the edema fluid of our patient is two times greater than values in any of the patients with ARDS previously reported. The elevated leukotriene B4 level is in the upper range of values found in some of the patients with ARDS of other etiologies (4). In the previously reported study (4), the level of leukotriene D4 in pulmonary edema fluid was significantly associated with the degree of increased vascular permeability as measured by the concentration of albumin in the edema fluid. This suggests the possibility of a primary causative relationship between leukotriene D4 and the alveolar–capillary leak, and indeed intravenous leukotriene D4 administered to dogs has been shown to produce noncardiogenic pulmonary edema (7).

The etiology of the pulmonary edema in the present case is not known. Although no wedge pressure was recorded prior to volume resuscitation, the mean wedge value of 17 mm Hg after rapid infusion of 9 L of fluid over 45 min, together with the markedly elevated protein and albumin content of the edema fluid, suggest that an alveolar–capillary leak was likely involved. This condition may have been related either to a hypersensitivity reaction to fresh frozen plasma or to the effects of extracorporeal circulation on plasma mediators of inflammation. Cardiopulmonary bypass has been shown to increase peripheral arterial plasma levels of thromboxane, prostaglandin F1, and complement (8), and to alter the pulmonary extraction of prostaglandin E1, norepinephrine, and 5-hydroxytryptamine as measured in pulmonary artery and left atrial blood samples (9). Several of these latter substances may potentiate the effects of leukotrienes on vascular permeability (6), although the direct effects of CPB on leukotriene extraction have not been examined.

The above findings allow for speculation concerning the use of inhibitors of the lipoxygenase pathway in arachidonic metabolism in the prevention and therapy of ARDS. The role of steroids as inhibitors of arachidonic acid metabolism in this context remains controversial (10,11). Use of specific leukotriene inhibitors, however, has shown considerable promise in prevention of anaphylactic responses in bronchi of atopic patients, as well as in vivo with asthmatic monkeys (6). Similar therapeutic trials have not yet been conducted in experimental models of increased lung vascular permeability.

This case report presents the finding of high levels of leukotrienes in the pulmonary edema fluid of a patient after cardiopulmonary bypass. The data presented are consistent with data from other studies and have important clinical implications.

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Herpes Zoster and Reflex Sympathetic Dystrophy

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Reflex sympathetic dystrophy (RSD) is a common disorder occurring after several conditions, including even minor trauma (1). Reports of RSD associated with herpes zoster infection are quite rare in the literature (2). We report on an 80-yr-old female who developed this syndrome after an attack of herpes zoster.

Case Report

The patient presented to our Pain Management Center with a 4-month history of left arm pain, hyperesthesia, and decreased mobility of the left wrist and hand joints. Her medical history included a chronic seizure disorder (petit mal type) that was well controlled with phenytoin, 100 mg, three times a day, and phenobarbital, 30 mg, once a day, and mild degenerative joint disease involving both hands treated with ibuprofen, 800 mg alternating with 400 mg, four times daily.

The patient reported that 4 months previously she had noted onset of burning pain in her left neck, shoulder, arm, and hand which was followed by the appearance of large vesicular eruptions over this same distribution. The disability involving her limb was initiated with this episode. She was admitted to her local hospital for 2 weeks where herpes zoster involving the C-7,8 and T-1 dermatomes was diagnosed. During that period she started a 21-day course of prednisone therapy with gradually decreasing doses. Initially she also received pentazocine, 50 mg every 8 hr, for control of pain. Later she used acetaminophen with codeine, 30 mg as needed, with some relief of her discomfort.

As the herpes zoster infection resolved, she reported that her arm became progressively more painful and her fingers gradually became flexed into a tight closed-fist position. The patient had to support her left arm while walking and to rest it on a pillow when sitting or supine. The weight of the bed sheets caused her discomfort when they touched her hand. She reported that her hand had been swollen during her hospital stay and that the clenched fist posturing of her hand receded only to be replaced by inflexible extension of the digits.

Two months after onset of the herpes infection, therapy consisting of nadolol and transdermal nitroglycerin was initiated for hypertension and symptoms that could be attributed to coronary artery disease. Within 2 weeks she developed congestive heart failure and mild pulmonary edema. The nadolol was discontinued, and furosemide, 20 mg twice a day, was begun.

Evaluation in our pain center revealed a patient with a swollen, pale, cyanotic left forearm and hand that were both protected with a towel. The skin was glossy, the skin and nails were dystrophic in appearance and the venous architecture of the left hand was diminished compared to the right hand. Interosseus muscle wasting was obvious, the fingers were in extension, and the patient was barely able to move her digits. The hand was unduly sensitive to light touch. The skin temperature of the thumb was 2.4°C higher on the affected hand than on the contralateral hand (skin temperature can be higher or lower than the unaffected side (3)), and forearm circumference was 3 cm less. A diagnosis of reflex sympathetic dystrophy was made and presumed to be secondary to her recent, painful herpes zoster infection.

Initial therapy consisted of blocks of the left stellate ganglion every other day for 2 weeks (6 injections) using 6 ml of 0.25% bupivacaine. Immediately after each stellate block, the patient had physical therapy from a specially trained hand therapist. The stellate ganglion blocks produced little measurable change in the temperature of her hand but caused a Horner's syndrome each time. There was a marked improvement in the patient's hand discomfort associated with an increase in the range of motion of the fingers so that she was able to manifest movement of her fingers from full extension to a half-closed fist position. Hand color improved, and there was a return to normal venous architecture after two stellate ganglion blocks.

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The bupivacaine blocks provided approximately 8 hr of pain relief, plus noticeable changes in skin color and joint range in motion in the affected area. Prior to each stellate block, progressive clinical improvement was noted by the patient and those caring for her in the pain center. At present she has full range of motion in her fingers, grip strength is improving, and she is starting to use her hand in daily activities for the first time in months.

Discussion

Reflex sympathetic dystrophy (RSD) is a debilitating and painful condition most commonly affecting but not limited to the upper or lower extremities. This syndrome is characterized by one or more of the following symptoms: 1) pain, often described as burning, and tenderness in the affected limb; 2) hyperesthesia; 3) swelling of the extremity; 4) vasomotor instability, typically manifest by temperature and skin color changes (the skin temperature has been reported to be either higher or lower on the unaffected side); 5) dystrophic skin changes; 6) osteoporotic bone changes, called Sudeck's atrophy; 7) limitation of joint movement with subsequent pericapsular fibrosis; and 8) muscle atrophy (1,3,4).

The etiology and pathophysiology of RSD remain unclear. Trauma appears to be a predisposing factor in the majority of cases (5), though the history of an inciting event is not always elicited. The severity of the injury does not necessarily correlate with the severity of the syndrome. RSD has also been reported in association with myocardial infarction, stroke, thromboembolic phenomenon, infection, cervical osteoarthritis, and other conditions. In a study of 140 patients with RSD, no causative factor could be identified in 15% of the patients (1).

Most commonly, treatment of RSD has consisted of sympathetic ganglion block and physical therapy. Other therapies have included β-blockade with propranolol (2), intravenous regional block with reserpine or guanethidine (6,7), stellate block in combination with systemic steroids (8), transcutaneous nerve stimulation (9), and oral nifedipine (10).

Reports of herpes zoster associated with onset of RSD are rare in the literature. Visitsunthorn and Prete reported a case of RSD involving the lower extremity 4 weeks after an outbreak of herpes zoster involving the S-1 dermatome (2). Dramatic improvement in their patient's symptoms was reported after 1 week of propranolol therapy initiated 6 weeks after the onset of leg discomfort. Interestingly, our patient reported no change in her RSD symptoms with the 2-week trial of β-blockade therapy for hypertension. Those who believe propranolol may improve RSD propose that by blocking the increased sympathetic nerve activity at the peripheral arteries and veins propranolol may relieve symptoms and cause the condition to regress.

Postherpetic neuralgia is a possible contributing factor in the symptoms of RSD in our patient. Colding speculated that the herpetic infection in the sympathetic ganglion increased the resting tone of the sympathetic nerves and this in turn caused a regional vasoconstriction of the tissue (11). He reported a series of 67 patients with postherpetic neuralgia, 50% of whom showed improvement with repetitive sympathetic blocks.

This case illustrates several of the prominent features of RSD and suggests that RSD may occur after herpes zoster infection. The role of postherpetic neuralgia in the development of this syndrome is not yet clear. Our patient appeared to be unresponsive to a short course of β-blockade and oral steroids, but improved with repetitive stellate ganglion blocks followed by aggressive physical therapy on an outpatient basis and continued at home.

The present case also serves as a reminder that patients presenting for consultation and treatment of RSD or postherpetic neuralgia may have symptoms of both diseases. Whereas sympathetic blocks are usually effective in the management of RSD, their use in postherpetic neuralgia may be associated with diminishing effectiveness since the neuralgic symptoms often persist for long periods of time. Thus sympathetic blocks may be of diagnostic value when such patients present for evaluation. Ordinarily patients with RSD will show progressive improvement with serial blocks, as did our patient, whereas those with postherpetic neuralgia may continue to complain of intractable pain and hyperesthesia until other, more effective therapy is initiated.

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Unilateral Hearing Loss after Spinal Anesthesia Treated with Epidural Blood Patch

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We report a case of acute onset of unilateral hearing loss after spinal anesthesia, which was successfully treated by means of an epidural blood patch.

Case Report

A 27-year-old female was admitted to the hospital for a repeat cesarean section. Past medical history was unremarkable, and physical examination and laboratory studies were essentially normal. There were no complications associated with pregnancy. She was scheduled for an elective cesarean section under spinal anesthesia. Approximately 1500 ml of Ringer's lactate solution was administered for prehydration. Lumbar puncture was performed without difficulty, employing a 25-gauge spinal needle. Spinal anesthesia was induced by the intrathecal injection of 8 mg tetracaine in 10% dextrose in water. During the surgical procedure an additional 1000 ml of Ringer's lactate solution was administered. Vital signs remained normal. Surgery was finished without incident. Estimated blood loss was 600 ml. The patient recovered from spinal anesthesia within 4 hr without apparent residual blockade.

On the second postoperative day she complained of a complete loss of hearing in her left ear. The hearing loss appeared to be postural. Conservative measures such as bed rest and fluid intake were instituted as well as psychological reassurance. On the fourth postoperative day, the hearing impairment persisted, and it was associated with dizziness and nausea.

A bedside hearing test disclosed a probable conduction defect in the low frequency range. The patient agreed to an epidural blood patch. Ten milliliters autologous blood was injected into the epidural space at the site of the previous lumbar puncture. Shortly after the blood patch was performed the hearing began to improve, and she recovered completely and permanently from the hearing loss about 1 hr later. The rest of the hospital course was uneventful. She was discharged without further complications 7 days after the operation and 3 days after the epidural blood patch.

Discussion

Vandam and Dripps (1) reported a 0.4% incidence of auditory complications occurring after spinal anesthesia. The auditory difficulties included decreased hearing, obstruction, plugging, popping, tinnitus, buzzing, and roaring. With few exceptions, these symptoms were associated with typical postural headache. One might assume that the auditory complications were secondary to a decreased cerebrospinal fluid pressure after lumbar puncture. It is known that there is an anatomical communication between the cochlea and the subarachnoid space through the cochlear canal. The perilymph that occupies the perilymphatic space in the cochlea resembles cerebrospinal fluid closely in its composition.

Hughson (2) demonstrated that a decrease in cerebrospinal fluid pressure is associated with a decrease in intralabyrinthine pressure followed by a functional inability of the ear to transmit high tones. Hence a decrease in cerebrospinal fluid pressure must be implicated for the hearing loss in the present case. The epidural blood patch could be an effective therapeutic measure for the auditory complications after spinal anesthesia as described in this case report, the first we have been able to find on this subject in the literature.

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Letters to the Editor

Naloxone–Morphine Synergism: Support for Dual System Hypothesis of Pain Perception

To the Editor:

We read with interest the recent paper by Dailey et al. on the use of a combination of intravenous naloxone and intrathecal morphine for pain control during labor (1). The area of particular interest to us in this paper refers to Figure 3 where the pain relief after intrathecal morphine was recorded for the subsequent 8 hr in both naloxone and saline control groups by independent investigators. The histograms portrayed show that initially and for the next 4 hr the control saline group demonstrated better pain relief than the naloxone group. However, from the fifth to the seventh hour, inclusive, less pain was apparently experienced by the naloxone group, whereas at the eighth hour both groups showed similar degrees of analgesia. It would therefore appear that the combination of morphine and naloxone not only provided better analgesia but that this analgesia began 5 hr after administration of the morphine. This unexpected analgesia produced by a pure opioid antagonist (at the low doses used) (2) and after the considerable time lag is not further commented on by these authors other than to say that naloxone did not diminish the morphine analgesia. We feel these findings are significant enough to require additional explanation.

This apparent paradoxical synergism between morphine and naloxone with regard to analgesia may not be such an unusual phenomenon because buprenorphine, a partial agonist, has similar synergistic effects when combined with either naltrexone (3) or naloxone (4).

We have also shown a similar synergistic analgesic effect of naloxone when combined with either other nitrous oxide (5) or other opioids (e.g., morphine (6)).

Previously, we have developed a hypothesis (dual system hypothesis of pain perception) in which we attempt to explain these paradoxical findings on the basis of the existence of two opposing opioid systems, one analgesic, the other hyperalgesic (5–8). The existence of a hyperalgesic opioid system has been demonstrated experimentally by Wu et al. in the pontine medullary area (9).

In the work of Dailey et al. (1), initially the naloxone would have tended to inhibit the morphine analgesia at the spinal cord level, whereas some hours later, the morphine would have had time to diffuse to the brain, at which point synergism is shown between naloxone and morphine (see Fig. 3 of Dailey et al. (1)). On the basis of our hypothesis, involving differential sensitivities to naloxone of the two opposing opioid systems, it would appear that the hyperalgesic system was now depressed relative to the analgesic system, thereby reinforcing the action of morphine. The fact that the morphine required some time to diffuse upward to the brain is consistent with the observed period of analgesia (5–8 hr) and is borne out by the finding that nausea and vomiting occurred around this period (1).

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Diazepam and Free Plasma Bupivacaine Concentration

To the Editor:

I wish to bring to the attention of your readers some contradictory statements in the report by Denson et al. (The influence of diazepam on the serum protein binding of bupivacaine at normal and acidic pH. Anesth Analg 1984;63:980–4).

The authors have concluded that the administration of diazepam during a toxic reaction to bupivacaine would not be expected to alter free bupivacaine concentration. At the same time they speculate that diazepam displaces bupivacaine from substantial tissue stores, that is to say, the volume of distribution (Vd) of bupivacaine is reduced.

We know that

$$\mathrm{Vd} = \frac{\text{Amount of drug in body}}{\text{Concentration in blood}}$$

or

$$\text{Concentration in blood} = \frac{\text{Amount of drug in body}}{\mathrm{Vd}}.$$

One can clearly see that for a constant amount of drug in the body, reducing the volume of distribution will automatically increase the concentration of drug in the blood. If applied to the case of bupivacaine, an increase in free plasma bupivacaine concentration (assuming that plasma protein binding of bupivacaine is unchanged) would be expected on displacement of bupivacaine from the tissues. This possible outcome seems quite incompatible with the authors' statement, "thus, administration of diazepam during a toxic reaction would not be expected to alter free bupivacaine concentration."

The authors may wish to comment on this apparent contradiction.

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In Response

Although Dr. Burke's statements with regard to Vd are correct, the apparently contradictory statements to which he refers were misinterpreted, perhaps due to taking the statements out of the sequence in which they were originally presented.

The primary purpose of our study, as stated in the introduction, was to determine the influence of diazepam on the *serum* protein binding of bupivacaine. With this in mind, no alterations in free bupivacaine concentrations were observed in the presence of diazepam, leading us to the conclusion, "thus, administration of diazepam during a toxic reaction to bupivacaine would not be expected to alter free bupivacaine concentration". We anticipated the reader would restrict this conclusion to a displacement from serum protein binding sites because this was all that was determined in this study.

A secondary goal of our study was to attempt to explain the reported decrease in elimination half-life of bupivacaine in the presence of diazepam described by Giasi et al. (1). As noted in our original paper, half-life is a secondary parameter dependent on total clearance and volume of distribution, as shown in the following equation:

$$t_{1/2} = \frac{0.693 \times \mathrm{Vd}}{\mathrm{CL}}.$$

It is readily apparent that the reduction in half-life can be explained by either an increase in clearance or a decrease in volume of distribution. Because clearance for bupivacaine is proportional to the free fraction of drug in blood, and because no alteration in free drug concentrations were observed, one would presume coadministration of diazepam would not alter bupivacaine clearance. Therefore the remaining possibility to explain the results of Giasi et al., as stated in the last paragraph in the paper, is a reduction in the volume of distribution. This led to our suggestion that perhaps diazepam would displace bupivacaine from tissues, reducing the volume of distribution, resulting in an increase in total concentration as well as a transient increase in free concentration, as illustrated by Dr. Burke. As stated in our paper, a significant displacement of bupivacaine from tissues could be of clinical significance. We also stated in our manuscript that this was beyond the scope of the study being reported and that studies designed to address this hypothesis were currently in progress.

Thus the two statements from our paper questioned by Dr. Burke are not incompatible when taken in the order of presentation. We apologize for any confusion we may have caused the reader.

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Position and Spread of Spinal Anesthetic Solutions

To the Editor:

The review by Greene, "Distribution of Local Anesthetic Solutions within the Subarachnoid Space" (1), tables 25 factors that can possibly influence the distribution of such solutions. The anatomic configuration of the spinal column is considered, and the work of Smith (2) is quoted to substantiate this influence. Unfortunately, he is misquoted. Smith reported a study of two groups of patients. Fifty received a "normal" dose of tetracaine in 5% dextrose (10–14 mg depending on height) and were randomly allocated to lying supine with either the legs extended or with the legs flexed for 2 or 3 min after being turned from the lateral decubitus position. The level of block was assessed at the start of the surgical procedure, presumably by the author, who also probably administered the drug. Consequently, the study was not "blind," and the author's findings may have been influenced by his hypothesis.

Nevertheless the findings showed that if the knees were kept up, and hence the lumbar lordosis was flattened, then a unimodal distribution of block level resulted, with a modal value at T9. In the patients who lay with the legs flat, a bimodal distribution was seen: some patients had block levels at T9, but more commonly the block extended to the T4. In these patients, therefore, the presence of the lumbar lordosis had resulted in a more cephalad spread of the local anesthetic—"downhill" from the lumbar lordosis into the thoracic region. This is contrary to the statements in Greene's review (1) that elimination of the lordosis may *increase* the cephalad spread, and exaggeration may decrease the spread. Because Smith's study (2) is the only study of this topic that we know of, the further statements in this section of the review must be hypothesis only. We are presently conducting a controlled, random study of this phenomenon with an assessor who does not know the prior position of the patient. We shall report the results after analysis at the end of the study. If they confirm the findings of Smith, it is clear that many studies of hyperbaric anesthetic solutions for subarachnoid block may have to be reappraised because of the nonnormal distribution of the data.

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Topical Tracheal Anesthesia can be Administered through a Catheter Attached to the Endotracheal Tube

To the Editor:

Care of patients requiring tracheal intubation for ventilatory support in the postoperative period is particularly challenging when one wishes to minimize the amount of sedation required to assure that the endotracheal tube (ETT) will be tolerated, especially in head trauma patients when assessment of the mental status is essential. Instillation of a local anesthetic through the ETT to obtain topical anesthesia of the trachea is often unsatisfactory. We have therefore modified the currently used ETT by firmly attaching a long #22 Teflon catheter with cyanoacrylate ester (a bonding substance used in dental/oral surgery) to the side of the existing catheter used for inflating the ETT cuff. The distal tip of catheter at the proximal part of the ETT cuff is sealed, and six side holes spaced evenly from its union with the ETT to the distal end are made, each hole facing in a different direction. With this extra catheter attached to the ETT, topical anesthesia of the entire upper airway can be achieved after the ETT is placed in the trachea by injecting a suitable amount of local anesthetic solution (4% lidocaine solution without preservative, 2–4 ml depending on patient's body weight) through the extra catheter. During prolonged surgical anesthesia in head and neck surgery, topical tracheal anesthesia can also be a useful adjunct to general anesthesia, and even in certain types of short operations such as herniorrhaphies, where bucking or straining on ETT is to be avoided, excellent topical tracheal anesthesia delivered through the catheter can reduce the irritation caused by the ETT in the trachea. We have used the modified endotracheal tube for the last 4 months in ten patients in the intensive care areas and during transportation of patients. Lidocaine solution is instilled through the catheter at no less than 3-hr intervals. Most of the patients require only two–three injections in a 24-hr period. There have been no instances of catheter separation or toxic responses to the lidocaine instillation. This type of catheter has proven to us especially useful in minimizing tracheal irritation by ETT during transportation of patients. Presently we are asking an ETT manufacturing company to incorporate the catheter into the body of ETTs.

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Reducing the Cost of Using Neuromuscular Relaxants

To the Editor:

Neuromuscular blocking agents are part of our anesthetic armamentarium. With the introduction of two new nondepolarizing neuromuscular relaxants, atracurium and vecuronium, the cost of obtaining muscle relaxation during surgical procedures is skyrocketing, as recently shown by Aldrete and Hendricks (1). One should bear in mind, however, that when combining two nondepolarizing agents, such as metocurine and pancuronium, the total amount of drug used may be less due to their potentiating effect (2). As a consequence the cost may also be less. For example, considering the same prices as those published (1), it can

Table 1. Amount of Drugs Used and Total Cost Using Three Different Techniques for Intubation in 12 Patients

Patient	ASA	Sex	Weight (kg)	Anesthesia duration (hr)	Intubation (mg)			Maintenance (mg)		Total (mg)		Cost (dollars)
					P[a]	M[a]	S[a]	P	M	P	M	
1	I	F	73	3.75	1.5	6.0	—	0	0	1.5	6.0	2.80
2	II	M	69	7.17	1.4	5.6	—	0.6	2.4	2.0	8.0	3.73
3	III	F	75	11.42	1.5	6.0	—	2.9	11.6	4.4	17.6	8.21
4	I	F	57	1.67	0.2	0.8	100	0.4	1.6	0.6	2.4	1.35
5	II	F	82	2.17	0.2	0.8	100	0.6	2.4	0.8	3.2	1.72
6	I	F	55	4.58	0.2	0.8	100	1.5	6.0	1.7	6.8	3.40
7	II	F	85	5	—	—	80	0.9	3.6	0.9	3.6	1.68
8	II	F	50	6.75	—	—	50	1.2	4.8	1.2	4.8	2.24
9	III	F	70	7	—	—	60	1.8	7.2	1.8	7.2	3.36
10	III	M	204	8	—	—	100	1.8	7.2	1.8	7.2	3.36
11	II	F	70	8.42	—	—	40	1.8	7.2	1.8	7.2	3.36
12	III	F	50	11.17	—	—	60	2.1	8.4	2.1	8.4	3.91

[a] P, pancuronium; M, metocurine; S, succinylcholine.

be calculated for a 70-kg man that by using pancuronium and metocurine (ED$_{95}$ of 0.018 and 0.072 mg/kg (2), respectively for the combination), the cost can be reduced by 66 to 71% ($6.91 if pancuronium were used alone, $8.02 if metocurine were used alone, compared to $2.35 with the combination) for one hour of anesthesia. The experience presented here with 12 patients (Table 1) shows that the actual cost may be even lower. Depending upon the technique used for intubation, an 11-hr procedure requiring muscle relaxation may cost $8.21 if the combination was used without succinylcholine (patient 3) or $3.91 if succinylcholine was used for intubation (patient 12). The amounts of drugs used and total cost for each patient are shown in Table 1. By carefully titrating the maintenance dose (0.2 mg pancuronium and 0.8 mg metocurine) and using a peripheral nerve stimulator, there may be no need to reverse the neuromuscular block. In fact none of the patients in the table required reversal. Avoiding the use of neostigmine and atropine will further reduce the cost of providing muscle relaxation.

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Intravenous Caffeine for Postdural Puncture Headache

To the Editor:

In view of recent articles (1,2) advocating the immediate use of epidural blood patch (EBP) for the treatment of postdural puncture (PDP) headache, we feel compelled to bring attention to an alternative therapeutic modality. The method of treating PDP headache we are referring to is that of the intravenous administration of caffeine sodium benzoate. Though this method has been known to the medical profession since the mid 1940s, it still is not in routine use, a fact that, in view of its effectiveness and low morbidity, we find bewildering.

Caffeine sodium benzoate (CSB) in doses of 500 mg has been shown to alleviate PDP headache in about 70% of patients and has helped to reduce the degree of suffering in a higher proportion (3,4,5). We recommend the treatment of PDP headache with CSB prior to the consideration of EBP. In our opinion, EBP should be kept as a second line method and should only be used if all other regimens fail. Our reasons for wishing to keep EBP as a secondary alternative are those mentioned in a recent publication by Crawford (6); namely, the uncertainty about the possible long-term sequelae of the procedure, and the more immediate risks of instilling autologous blood into the epidural space, including the risk of infection, cord compression, and a second dural puncture.

In his review of 300 cases of EBP, Crawford reports that, in 17 patients returning for repeat epidural analgesia after previous EBP, approximately one quarter failed to get initial satisfactory analgesia. Furthermore, in one case a possible mechanical obstruction was thought to be present. This latter case, together with another recent case reported by Rainbird and Pfitzner (7), and an earlier similar personal experience (APJ), suggests that instilling autologous blood into the epidural space may not be as innocuous as it is said to be, something many neurosurgeons have been saying for a long time.

The protocol under evaluation by our institution provides for the rehydration of patients with PDP headaches with 2 L of intravenous fluid, the first of which contains 500 mg CSB. This is given over 1 hr, the second liter following over the subsequent 2 hr. The patient's headache is reevaluated after this course of treatment. If cured or improved so much that there is no request for further treatment, then the patient is discharged. If the first CSB course is insufficient, then, following a 4-hr interval, a second course of CSB is given (repeat of the first), and again patients are discharged if pain free. If, however, the second course of CSB proves ineffective, patients are then offered autologous EBP. In our experience to date, out of eighteen patients the first or second dose of CSB relieved PDP headache in approximately 75% of cases (14 out of 18), thus making the routine use of EBP as an initial treatment unnecessary.

Assuming the final results of our ongoing study show a similar success rate, we believe a significant proportion of patients who develop PDP headache can be safely treated with a more conservative approach, thus eliminating the potential morbidity of autologous epidural blood patching.

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Thoughts on Spinal Anesthesia Failures from a Non-Teaching Hospital

To the Editor:

I was interested in the statistics quoted by Levy et al. (Anesth Analg 1985;64:705–10) on failed spinal anesthetics in a university hospital. They speculate about the many possible causes for a 17% failure rate, defined as the need to add inhalation anesthesia to the block. They mention the absence of data from nonteaching hospitals and wonder if the high failure rate might even be due to unknown, inherent, technical factors.

I practise in a large HMO on the West Coast with a group of nine anesthesiologists and 19 CRNAs. The MDs do all the spinal anesthetics. As part of my recent task of peer review, I have access to the pertinent data for our hospital. In the months of April and May this year, we did 137 spinal anesthetics. By the criteria of Levy et al., we had seven failed spinals for a 5% failure rate, so I cannot believe that a high failure rate is inherent in the technique. Several thoughts do, however, come to mind.

Their study mentioned 100 *consecutive* spinals done over a one year period. Does that mean that there were only about 100 spinal anesthetics done over that time? That, it seems to me, is far too few for residents to become expert.

Almost half of the spinals were done with #22-gauge needles. Again, this suggests lack of experience as a cause for failure. Expert wielders of the spinal needle almost uniformly use #25- or #26-gauge needles.

The study did not mention the source of tetracaine used. Failure rates go up when the commercially prepared trays are used close to the date of expiration.

A brief analysis of our seven failures is interesting. One failure was in an elderly man in whom free flow of CSF was obtained yet no block ensued. The same sequence had occurred during his previous spinal attempt a month before.

One failure was due, I believe, to an inadequate dose of tetracaine. One was a technical failure to obtain any CSF at all, and one was failure to get a free flow of CSF. The remaining three failures to obtain a block were done by the most recent and least experienced member of our group.

Levy et al. are correct in saying that it is critical to get freely flowing CSF before and after injection of drugs. This is a more meaningful sign when using a #25-gauge needle. I have almost never failed to get a solid block when I get back free flow through a #25 needle. I think that the larger bevel of the #22 needle can be half in and half out of the dura mater, thus giving a false impression of complete intrathecal placement.

However, I believe that the most important factors in reducing the failure rate are practice and more practice, and being very particular about the small details of midline placement and free CSF flow.

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In Response:

We thank you for the opportunity you have given us to respond to several points raised by Dr. O'Keeffe. We begin the letter by answering the valid question raised by 100 consecutive spinals in the third paragraph.

Our study selected one hundred consecutive spinal anesthetic procedures covering the 2-month period from March to April 1983. However, as we noted, if patients had received more than one spinal anesthetic, only the first one was included in the study. In 1983 we performed 675 spinal procedures out of a total of about 9500 anesthetic procedures, or about 36 spinals per resident per year. We agree with Dr. O'Keeffe that 36 spinals per resident per year is certainly far too few for residents to become experts.

Most of the disposable spinal trays used at the time provided only #25-gauge needles, and it is conceivable that in many of these patients the anesthesia residents attempted at first to use #25-gauge spinal needles. However, when these initial attempts failed to locate the subarachnoid space there was a tendency for residents or attending anesthesiologists to switch to #22-gauge needles. In any case, our data, and the data of Moore (1) did not demonstrate a difference in the failure rate based on needle size.

Only rarely in today's practice is failure to produce anesthesia the result of an injection of local anesthetics which are no longer pharmacologically active (2). At the time of this study we used a commercially available solution of tetracaine in a 1% isobaric isotonic solution. There was no failure reported that included the use of an outdated spinal tray. Members of our Equipment Committee monitor supplies and regularly discard commercially prepared trays from our storage rooms as trays near the expiration date. On the other hand, because some trays are discarded, others might be supplied to the operating room near the expiration date to make sure they are used, as part of normal stock rotation.

In a recent study Van Deripe and Yim (3) examined the source of tetracaine as an important variable in the effectiveness of spinal anesthesia. These authors tested 1% tetracaine ampuls for local anesthetic activity and toxicity after about 10 months storage and failed to relate spinal anesthetic failures, delayed and/or incomplete anesthesia, or postspinal paraplegias to the use of partially hydrolyzed or "crystal containing" solutions. Thus this study does not support the statement by Dr. O'Keeffe that "failure rates go up when commercially prepared trays are used close to the date of expiration."

Before our data can be compared with data from other, nonteaching hospitals, a clear definition of failure of spinal anesthesia is in order. Failure of spinal anesthesia is defined in our paper as the need to add inhalation anesthesia to the block primarily for the relief of persistent pain from whatever cause and to control associated restlessness and movements. This includes cases of complete failure; partial, incomplete, or unilateral anesthesia; and short or delayed anesthesia. In the cases described as failures, the spinal anesthesia 1) was insufficient to permit operation to begin, 2) it failed to produce anesthesia for the usually expected time period, or 3) it wore off before the surgical procedure could be completed.

Since we published our study, we have continued to search for causes of failure in these 17 subjects and made new observations in many other patients undergoing spinal anesthesia at this institution. The problems we frequently encounter that lead to failure are usually subtle in nature. Three most common situations with a single-dose spinal failure are as follows: 1) partial or no analgesia after an apparently satisfactory block due to technical reasons; 2) inappropriate selection of agents resulting in duration of analgesia shorter than the duration of surgery; and 3) inappropriate selection of the technique due to improper perioperative planning. We plan to submit this study describing causes and mechanisms of failure of spinal anesthesia in a university hospital (Part II) at a future date.

Our study examined the relationship between the failure rate and the experience of the practitioner. We saw no difference in the failure rate between first-year residents, second-year residents, and attending anesthesiologists. This suggested that practice in and of itself did not necessarily decrease the failure rate and supported our conclusion that poor technique, errors in judgement, and unknown technical factors contributed to our high failure rate. On the other hand, if the attending anesthesiologist is only supervising and not performing the blocks routinely, his practice may also be suboptimal. We feel that anesthesiologists must obtain the proper technical skills during their residency and then maintain them throughout their practice lives, for without these skills practicing a technique incorrectly 1000 times will not improve the failure rate and will lead to the abandonment of an important form of anesthesia, i.e., regional anesthesia. I am happy to see that Dr. O'Keeffe's incidence of failure for these 2 months was less than ours, but 5% is still high if regional anesthesia is to be chosen as opposed to general anesthesia, which has a failure of induction rate of 0%!

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Axillary Artery Compression and the Prone Position

To the Editor:

Many operative procedures require use of the prone position. We report a case of an unusual and potentially dangerous complication—axillary artery compression.

A 63-yr-old, 110 kg man with a significant smoking history was scheduled for lumbar laminectomy. General anesthesia was induced, and the patient was turned and placed in the Georgia prone position with two large rolls to support the chest and pelvic area (1). The patient's outstretched arms were placed cephalad on armboards parallel to the table. A pulse oximeter (Nellcor) was placed on the left index finger to monitor oxygen saturation, and a blood pressure cuff was placed on the right arm.

After positioning, although blood pressure was stable, the oximeter alarm sounded, indicating low perfusion in the left index finger. The left brachial and radial pulses were found to be absent. Repositioning the left upper arm by adduction to a final position at a right angle to the chest wall resulted in restoration of pulses and accurate pulse oximeter readings. Review of the chest radiograph postoperatively showed no cervical ribs.

Although no published reports describe such a complication of the prone position, we feel that axillary artery compression can occur in the prone position if the arm is abducted too far at the shoulder, resulting in downward traction of the axillary artery by the humeral head. Compression can occur even in the absence of a cervical rib. Untoward sequelae can be easily avoided by periodically checking the radial pulses bilaterally when this position is utilized. In this case the use of the pulse oximeter to follow this patient's pulmonary status facilitated immediate diagnosis. Placing the oximeter on the side opposite the blood pressure cuff provides one with a continuous monitor of perfusion in both arms. Obese individuals with large outstretched arms may be more susceptible to this complication.

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Reference

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Esophageal Stethoscopes Can Reveal Light Anesthesia

To the Editor:

With the current trend toward shortening operating room stays and hastening recovery room discharges, anesthesiologists are keeping patients "lighter" during surgery. Though speeding emergence, light anesthesia courts the possibility of troublesome coughing, movement, or awareness. Using an esophageal stethoscope, I have observed an early sign of lightening of anesthesia. This sign is not mentioned in either of two modern descriptions of indicators of depth of anesthesia (1,2).

After tracheal intubation and initiation of mechanical ventilation, the esophageal stethoscope is inserted until half its length protrudes from the patient's mouth. During continuous auscultation, a muffling of heart and breath sounds, sometimes accompanied by swallowing noises, is usually the first sign that the patient is becoming lighter. I have learned to administer an intravenous drug promptly (usually thiopental) when the auscultatory muffling occurs. Otherwise the patient progresses to less subtle signs of light anesthesia within 1–2 min: "bucking," coughing, hiccoughing, or movement.

The auscultatory muffling precedes hypertension or tachycardia and has occurred during anesthesia conducted with either nitrous oxide–narcotic or halogenated anesthetics. It commonly occurs during deep (though not total) neuromuscular blockade. The sign is not rare; I have heard it during hundreds of cases over the last four years. It seems to have escaped mention in our literature.

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Morphine–Halothane Interaction Controversy

To the Editor:

I read with interest the recent article by Lake et al. on reduction in halothane MAC by morphine and alfentanil in rats (1). In this and in a previous article (2), the authors convincingly demonstrate that morphine and sufentanil are superior to alfentanil in their ability to reduce halothane MAC. I would like to attract attention to another aspect of the presented data that was not discussed in the article. "Almost complete anesthesia" with morphine and sufentanil used for reduction of halothane MAC in these two studies (1,2) in fact means that morphine (sufentanil) cannot completely substitute for halothane in achievement of the desired level of the index of anesthesia chosen by the authors. The authors used the tail clamp technique, a common technique not only for measurement of anesthetic action of general anesthetics, but also an even more common technique for assessment of analgesic action of opioids. There are many publications showing that morphine can completely block motor response to tail clamp in rats with an ED_{50} range from 2 to 10 mg/kg (3,4,5). Yet the authors could not produce a MAC (ED_{50}) level with morphine, 20 mg/kg, without at least 16% of halothane MAC. It appears that halothane inhibited morphine's classical effect on motor response to somatic noxious stimulation.

Interestingly, Murphy and Hug (6), using another species of animals (dogs), reported results that also may be indicative of morphine–halothane antagonism. In their experiments even 27 mg/kg morphine could not block movement response to the tail clamp without the addition of enflurane, 0.69% (end-tidal concentration). However, interpretation of their experiments is difficult because there are no data in the literature on morphine ED_{50} when used alone for blockade of motor response to the tail clamp in dogs (probably due to profound hypotensive effects of large doses of morphine in dogs).

In a recent study of morphine–halothane interaction in rats with the use of isobolographic method, we found that halothane in a small concentration antagonizes the antinociceptive effect of morphine (7). However, this was true only for the cardiac acceleration response caused by tail clamp. When movement response to tail clamp was studied, it was found that morphine, when given alone, was able to completely block the motor response to tail clamp (with ED_{50} and ED_{95} values of 6 and 8.5 mg/kg intravenously, respectively) and addition of halothane 0.5% (inspired) did not antagonize the effect of morphine.

The finding of Heckler and associates of "almost complete anesthesia" with morphine when halothane was used for MAC determination (2) is indicative of a morphine–halothane antagonism but only on the condition that the effect of morphine, 20 mg/kg subcutaneously, given alone is enough to produce motor unresponsiveness to the tail clamp in at least 50% of the animals. It is known that doses of morphine for blockade of motor response to tail compression depend to a very significant extent on the strength of the compression: up to fivefold difference in the dose of morphine (5). Therefore, the morphine ED_{50} values taken from other studies, as we tried to do in the above paragraphs, may be misleading. Probably the authors of the articles (1,2) are best qualified to solve the mystery of incomplete blockade of the tail clamp response with opioids when the level of anesthesia is measured by halothane MAC. Does this represent antagonism between opioids and inhalation agents commonly used together in anesthesia?

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In Response:

We appreciated the interest and comments from Dr. Kissin on our recently published work on the reduction of halothane MAC by morphine and alfentanil in rats (1). As he clearly describes, there are substantial differences in methodology among the published works describing requirements for inhalational anesthetics and analgesics alone or in combination. As Kissin et al. point out in their paper (2), blockade of purposeful movement and blockade of heart rate increase may be different components of anesthesia with inhibition of the movement response regarded as an anesthetic process, while abolition of heart rate increase, a sympathetic response, is a nonanesthetic process.

Our work measured only the reduction in anesthetic requirements, using the widely accepted tail clamp method with a supramaximal stimulus (3). The limitations of the clamping technique, specifically the problems of standardization of the point of application of the clamp and of altered sensitivity in subsequent testing have been previously addressed. MAC in the same animals has been shown to be constant with time and reproducible. These factors were controlled in our experiments, as previously described, by clamping sequentially from distal to proximal points on the middle one-third of the rat tail.

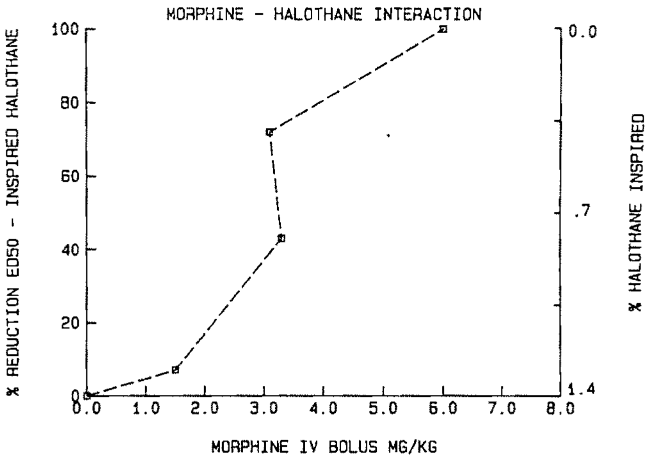

Figure 1. The reduction in the MAC of halothane produced by increasing doses of morphine in rats as replotted from the data of Kissin et al. (Morphine–halothane interaction in rats. Anesthesiology 1984;60:553–61.) It demonstrates a less consistent dose–response relationship than that presented in figure one of Lake et al. (Anesth Analg 1985;64:807–10.)

In addition to a standardized clamping method, a true measure of anesthetic requirement necessitates the measurement of alveolar anesthetic concentrations as carried out in our methods because of the similarity of alveolar concentrations to brain concentrations. In contrast, Kissin et al. measured inspired concentrations. Despite his use of an approximation method for the determination of anesthetic requirement (MAC), his dose–response curve for morphine is, in general, similar to our findings and demonstrates a reduction of MAC with increasing doses of morphine (Fig. 1). If Kissin's data are replotted using our coordinates, a less consistent relationship of dose and reduction in anesthetic requirement is seen than in our data.

The use of subcutaneous morphine injection in our experience produces consistent plasma morphine concentrations that were documented in our study; in contrast, Kissin used an intravenous bolus technique. The intravenous administration of a given dose, followed by an interval of 15 min before determination of animal movement, raises the question of constancy of plasma concentrations. Unfortunately, Kissin et al. did not measure the plasma morphine levels, so that we cannot compare responses. He also has not evaluated for changes in plasma morphine concentrations with time. Hepatic blood flow is known to decrease with halothane and hence should alter morphine plasma concentrations. Morphine concentrations were measured in our experiments, were stable, and were dose dependent.

In addition, in previous experiments we noted that Pco_2 increased to 69 mm Hg after an 8-mg/kg dose subcutaneously in a spontaneously breathing rat. With larger doses, (i.e., 20 mg/kg subcutaneously) a Pco_2 in the range of 100–200 mm Hg would be present. An increase in P_{CO_2} to these values would reduce MAC by 10–50% (4). This may account for the additional reduction in MAC seen in Kissin's spontaneously breathing animal at high morphine doses (100% MAC reduction). The P_{CO_2} in all of our animals was maintained at 40 mm Hg.

Changes in heart rate in response to tail clamp were not a part of our studies, so we cannot comment upon them in light of our work. However, the possibility that hypercarbia altered the cardiac responsiveness cannot be ruled out in Kissin's work. Hypercarbia is a well-known cause of tachycardia. The doses of morphine used by Kissin et al. in the heart rate experiments were higher than used in our experiments. In his evaluation, antagonism was noted only with a high dose of morphine and a low dose of halothane. The doses of 270–330 mg/kg in Table 3 of their paper are difficult to interpret in a spontaneously breathing animal model.

In summary, the clinical concurrence of our findings in animals with those of anesthetized humans suggests the continued validity of the determination of MAC and the additive effects of anesthetics and analgesics.

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Book Reviews

Update in Intensive Care and Emergency Medicine

J. L. Vincent, ed. New York: Springer-Verlag, 1985, 304 pp, $31.00.

This book represents the proceedings of the fifth International Symposium on Intensive Care and Emergency Medicine held March 26–29, 1985, in Brussels, Belgium. There are 65 chapters by 50 international authors, of which 13 are from the United States.

Most of the chapters are 3–5 pages long and represent a summary of more extensive oral presentations. The value of these brief summaries is quite limited to the reader who is intent on expanding his knowledge of such broad topics as "Pathophysiology of Acute Lung Injury" or "Nutritional support of the Critically Ill Patient." The major value of the chapters may lie with the bibliographies, which are usually current.

The book is not recommended to the physician who is new to Anesthesiology or Critical Care because of its absence of preliminary and explanatory information. Rather the book is recommended to the experienced clinician who wants to know briefly what other ICU physicians are writing and saying about a broad variety of Critical Care topics.

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Controlled Hypotension in Neuroanaesthesia

D. Heuser, D. G. McDowall, and V. Hempel, eds. New York: Plenum Press, 1985, 230 pp, $35.00.

This text is a summary of the proceedings of a multidisciplinary conference held in Tubingen, West Germany, in 1981 which considered the role of controlled hypotension (CH) in the clinical practice of neurosurgery and reviewed current concepts related to methods and cerebral metabolic and physiologic effects.

Five aspects of CH are presented: pharmacology and toxicology of the primary and adjuvant drugs; cerebral metabolism and blood flow; monitoring of cerebral electrical activity; neuropathology of complete and incomplete global ischemia; and clinical aspects, including a discussion of the efficacy of CH in facilitating neurosurgical procedures.

Because the book appears four years after the conference, it serves as an excellent summary of CH to that time. More recent areas of interest, e.g., the efficacy of isoflurane in CH and experimental data related to newer hypotensive agents such as urapidil and ATP (adenosine) are not included, although studies have appeared in the literature regarding these agents in the preceding and intervening years. The chapters devoted to electrophysiologic monitoring (EEG, evoked potentials) are an excellent summary of clinical and experimental data related to cerebral ischemia and may prompt the reader to pursue some form of objective monitoring of cerebral perfusion during CH in his own practice. Many illustrations demonstrate the utility of the cerebral function monitor, although its use in this country has not been widespread. Nevertheless, the relevant pathophysiologic correlates and clinical applications are well-presented. The metabolic and pathologic aspects of cerebral ischemia are clearly and completely summarized.

Experimental data regarding cerebral ischemia, particularly the deleterious effect of "glucose loading" on the severity of cerebral lactic acidosis and adverse neurologic outcome, are extensively documented and support the present practice of maintaining euglycemia in patients at risk for cerebral ischemia. Cardiopulmonary bypass and craniotomy patients, indeed, all anesthetized patients, may benefit from attention to blood glucose levels should cerebral ischemia develop unexpectedly.

The chapter about volatile agents and CH contains several figures demonstrating the effect of various antihypertensive drugs on blood pressure and intracranial pressure in severe head injury patients. Unfortunately, the chapter says very little about volatile agents. Instead one patient to whom four vasodilator drugs were given is presented, the sequence in which they were administered being unclear. In the initial figure, cerebral perfusion pressure (CPP) [mean arterial pressure (MAP)—intracranial pressure (ICP)] was very low prior to administration of sodium nitroprusside, and even lower afterward. There is no description of concomitant therapy or outcome in this patient with a Glasgow Coma Scale score of 5, but one would question the indications for such therapy in a severely compromised patient. Intracranial pressure may increase if cerebral vasodilation occurs or it may decrease if autoregulation is abolished; MAP will decrease and CPP will potentially be adversely affected with either ICP response. Cerebral vasodilators are not recommended for patients with severe head injuries.

Because there are no epidemiological studies regarding

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morbidity and morbidity related to CH during neurosurgical procedures, it is difficult to condemn or condone its use. The authors recommend careful consideration of patient selection and appropriate monitoring to maximize safety and efficacy.

Though there are several spelling and syntax errors throughout the text, readability does not suffer despite multiple authors. I would recommend this text for inclusion in neurosurgery and anesthesiology departmental libraries and for the personal libraries of neuroanesthesiologists.

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Effects of Anesthesia

B. G. Covino, H. A. Fozzard, K. Rehder, and G. Strichartz, eds. Bethesda, MD: American Physiological Society, 1982, 224 pp, $39.95.

This is a super book! One is reluctant to gush publicly, but in fact, the volume is superb. Superb in its choice of contributors and topics, well-written chapters, appropriate tables and charts, and pertinent and timely references.

There are three sections: effects of anesthesia on cell membranes and the molecular basis for anesthesia, effects of anesthesia on the respiratory system (ventilatory control, respiratory machines, pulmonary circulation, pulmonary gas exchange), and effects of anesthesia (general, regional, intravenous) on the circulation, a total of 15 chapters. The authors are expert on their topics; the self-citations found in each chapter are evidence not of vanity but of their expertise. As a result, though, each chapter is not an all-encompassing review but rather reflects to a large extent the author's research interests.

But be aware—though part of the American Physiological Society's Clinical Physiology Series, this book is hardly intended for the clinician without research interests and background. The book seems to be written more for physiologists with an interest in anesthesia more than for anesthesiologists with an interest in physiology. Understanding the material requires a knowledge of research techniques and ideas. But for one with this interest and background the book is superb.

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The Origins of Anaesthesia

Sherwin B. Nuland. Birmingham, AL: The Classics of Medicine Library, 1983, 1000 pp, $60.00.

This magnificently bound volume from The Classics of Medicine Library is as outstanding for its contents as for its appearance. In what surely must have been a labor of love for the medical historians at Yale University, Dr. Nuland has woven a tapestry of his narration interspersed with fine reproductions of original articles from the Anodynes of Antiquity, through Mesmerism and Hypnotism, Suspended Animation, Ether Frolics, and finally the contributions of Long, Morton, Wells, Warren, Simpson, and Snow. Considerable attention is given to the controversy over the discoverer of Sulphuric Ether, early press reports of its use, and even the censure of W. T. G. Morton by the American Medical Association. Of particular interest is the reproduction of Morton's brochure prepared for the surgeons at Massachusetts General Hospital to instruct them in the use of Ether.

Dr. Nuland's clear style makes for easy and fascinating reading. If the book has any flaw it is in the confusing arrangement of page numbers. The author's story carries its own page numbers as do the reproductions of original articles, and because these are interspersed through the narrative (although always in complete form) the result is rather confusing when seeking a particular subject or citing a reference.

Perhaps a master page numbering system at the bottom of each page would help avoid the confusion. I feel an index would also improve its value as a reference text. I hope the author and publishers will consider this when reprinting the book. It certainly ought to be reprinted and made available to the many anesthesiologists and medical historians who will appreciate and treasure it.

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Case Studies in Critical Care Medicine

Ray D. Cane and Barry A. Shapiro, eds. New York: Year Book Medical Publishers, Inc., 1985, 262 pp, $29.95.

The evolving speciality of Critical Care Medicine has seen a flood of texts in the last several years. Some of these books have attempted to be comprehensive, such as the "Textbook of Critical Care," presented by the Society of Critical Care Medicine. Other books have attempted to narrow in on more confined areas, such as the recent "The Pharmacologic Approach to the Critically Ill Patient." Few texts have taken a case study approach.

The book by Cane and Shapiro attempts to cover the more common ICU problems by applying didactic information to patient management through case study. Each chapter is structured in an identical fashion. The reader is given preliminary information such as data on gram negative bacteremia in Chapter 11. Next a case is presented with preliminary, admitting information. This is followed by further didactic information as it applies to the case. Further case information is presented with detailed points about therapy. More discussion about patient management follows. This pattern of case information followed by discussion repeats through the chapter until the patient is discharged and the topic has been covered.

The book is written primarily by the anesthesiology and internal medicine faculty of Northwestern University. Despite the contributions of 15 different authors, there is amazing similarity in the structure of each chapter, which is certainly a tribute to the editors of the book.

Even though there is great similarity in chapter style and structure, there are marked differences in the quality of information presented in various chapters. The discussion of head injury and intracranial hypertension by Tod Sloan and Antoun Koht is excellent and quite complete. Their bibliography is up to date and extensive. Other chapters cover important areas in a perfunctory fashion with an inadequate and out of date bibliography.

On the whole the book is quite good and worth reading, especially for the anesthesiology resident. It would seem this book would make a good teaching tool for program directors developing a critical care curriculum for residents.

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Recent Advances in Anaesthesia and Analgesia, (number fifteen)

R. S. Atkinson and A. P. Adams, eds. New York: Churchill Livingstone, 1985, 231 pp, $25.00.

This book is comprised of twelve separate chapters covering a variety of topics ranging from anesthetic agents and ventilatory techniques to a discussion of malignant hyperpyrexia. The title is somewhat misleading. Many of the chapters seem to be primarily a restatement of known facts and considerations rather than a presentation of new information. This is especially true of the chapters concerning airway obstruction in children, aspects of thermal injury, and morbidity and mortality. The chapter on isoflurane is fairly superficial in its discussion but is well organized, and the comparisons of isoflurane, halothane, and enflurane are informative. The chapter on new muscle relaxants is generally enlightening and contains useful and fairly current information. The statement that "the Hofmann elimination is the main pathway of degradation . . . ," has been questioned by Nigrovic (1) and others. There is also no mention of possible toxic metabolites such as acrylates with atracurium. The chapter on intravenous induction agents omits such agents as thiamylol and the benzodiazepines. Disoprofol is no longer formulated in Cremophor EL but is now formulated in an egg lecithin emulsion. These examples illustrate how rapidly information changes in anesthesia.

The chapter on synthetic analgesics has a well-written section on the mechanism of pain and analgesia. The chapter on high-frequency ventilation is especially well done and contains a simple and clear comparison of the mechanics of IPPV, HFJV, and HFO. The discussion of clinical applications is astute. The chapter on calcium channel blockers contains informative sections on calcium mechanics and clinical considerations. The chapter on the gastric acid problem contains a knowledgeable discussion of the various considerations of gastric acid production and treatment. Finally, the chapter on malignant hyperpyrexia has detailed sections on the biochemical basis of MH and associated disease states.

The chapters of the book vary greatly in their quality of information, but many of them contain very useful and current knowledge of anesthesia and analgesia. This text will be most suited for nonphysician anesthetists and those physicians still in training rather than as a reference book for academic or experienced anesthesiologists.

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Reference

1. Nigrovic V, Auen M, Wajskol A. Enzymatic hydrolysis of atracurium in vivo. Anesthesiology 1985;62:606–9.

Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

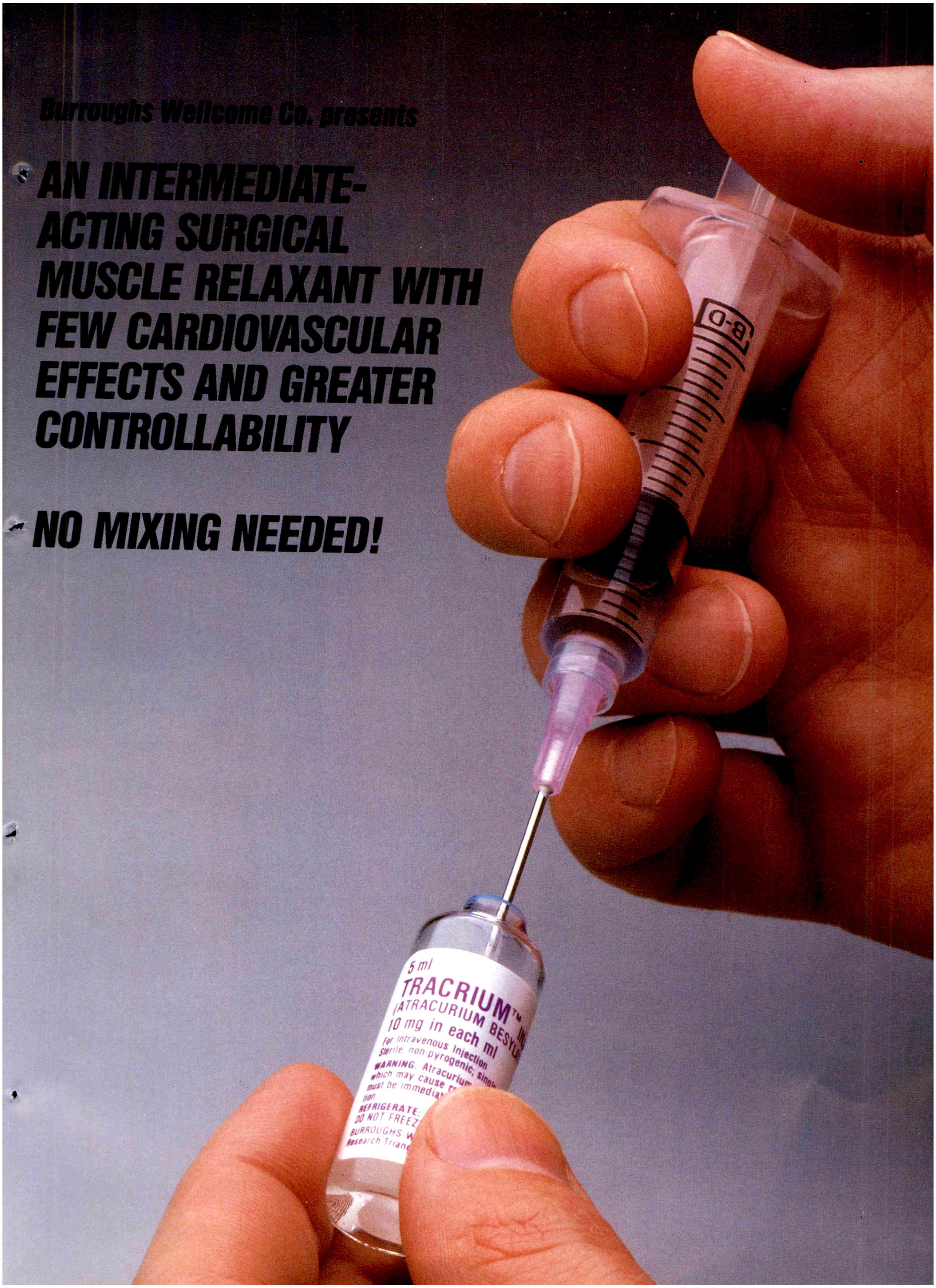
Classical Anesthesia File. D.M. Little Jr. Park Ridge, IL: Wood Library-Museum, 1985, 335 pp, $35.00.

Current European Anaesthesiology, Volume 1. R.M. Jones, ed. New York: John Wiley and Sons, 1985, 297 pp, $24.50.

Acid–Base Regulation and Body Temperature. H. Rahn, O. Prakash, eds. Boston: Martinus Nijhoff Publishers, 165 pp, $39.90.

Special Problems in Pediatric Anesthesia. R.I. Godinez, ed. Intl Anesth Clin vol 23, no 4. Boston: Little Brown & Co., 1985, 235 pp, $24.00 for single or $53.00 for four issues per annum.

The Pregnant Surgical Patient. J.M. Baden, J.B. Brodsky, eds. Mt. Kisco, NY: Futura Publishing Co., Inc., 260 pp, $36.00.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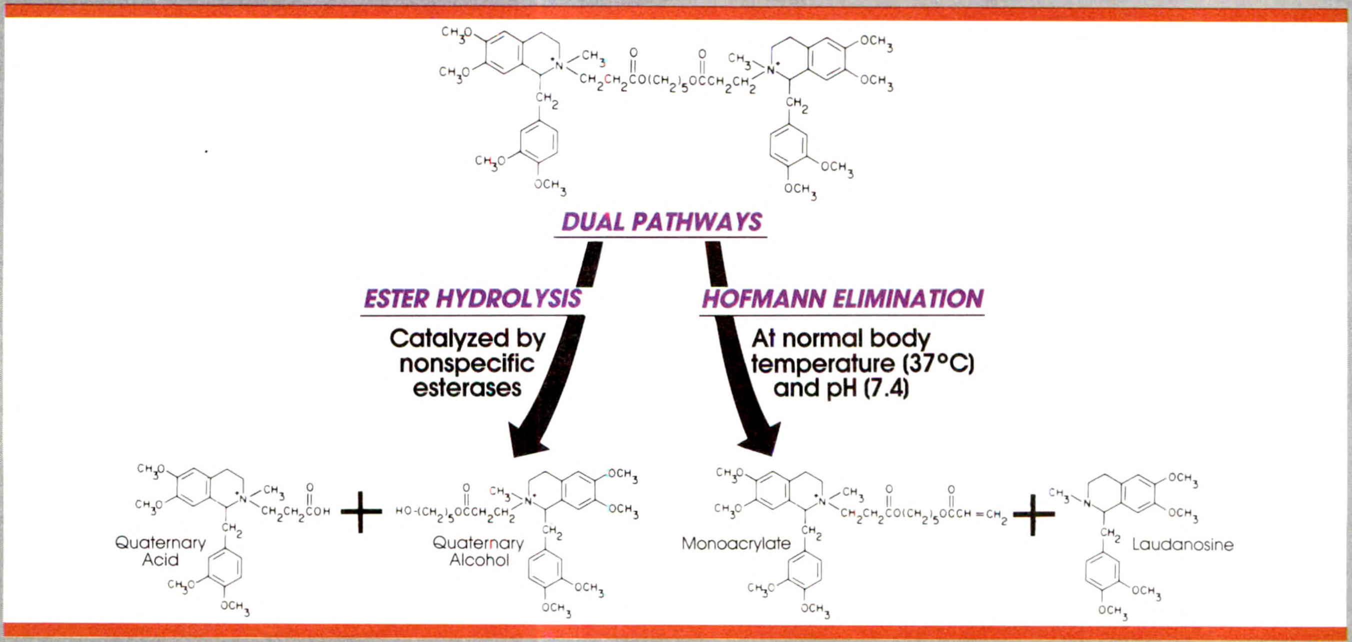


☐ *Tracrium® Injection (atracurium besylate) is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:*

1 *Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH*

2 *Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required*

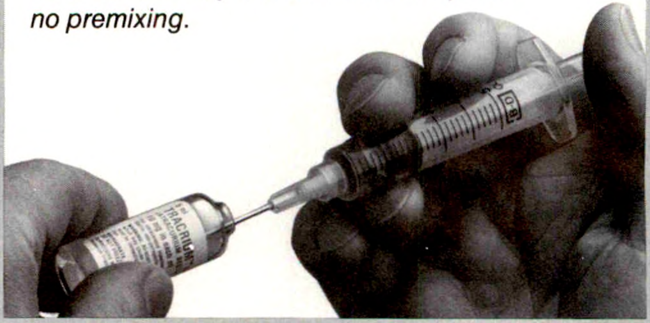
These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."[1]

"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."[2]

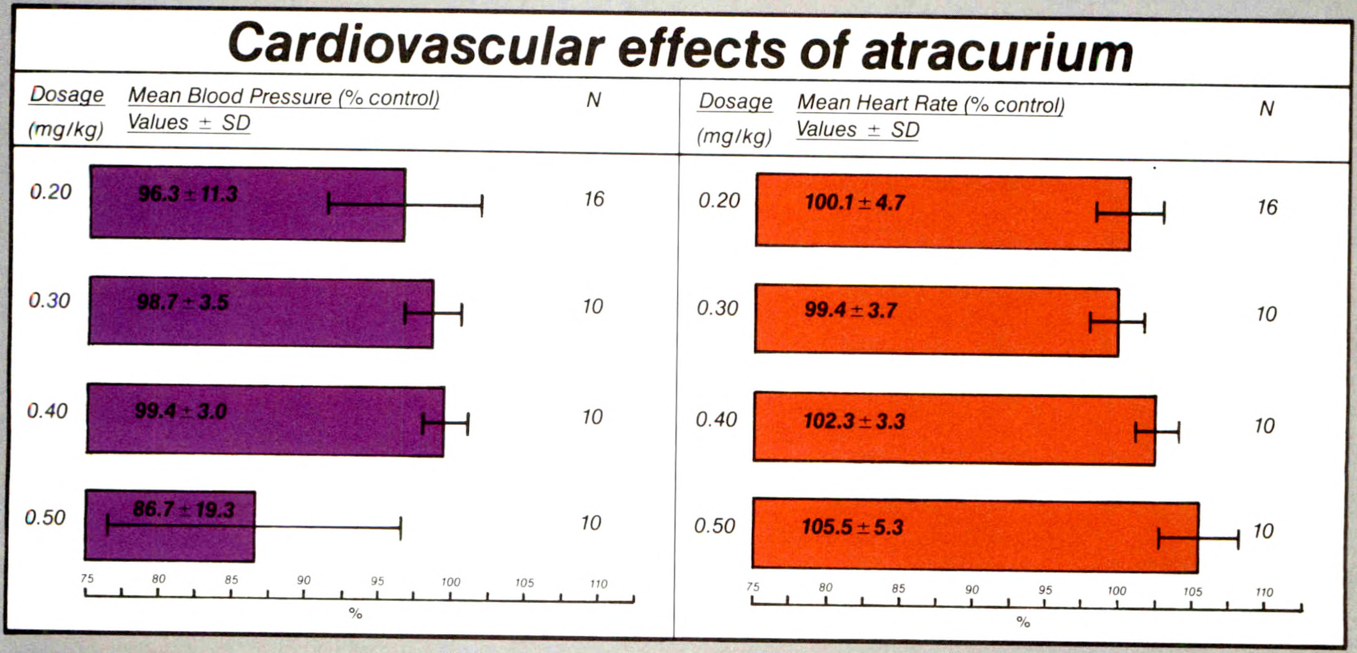
Convenient and Ready to Use

Tracrium is easily administered—requires no premixing.



Few Cardiovascular Effects at Recommended Dosages

☐ *Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.*



Adapted from Basta et al.[3]

No Cumulative Effects Upon Recovery, After Multiple Doses

☐ *Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time*

☐ *Once recovery begins, it is relatively rapid and independent of dose*

☐ *This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable*

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."[1]

Minimal Histamine Release

☐ *Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine*

☐ *Clinically significant histamine release occurs well within the clinical dosage range (at ED_{95}) for curare, at the upper limits of the clinical dosage range (at 2 × ED_{95}) for metocurine and outside the clinical dosage range (at 3 × ED_{95}) for atracurium[4]*

☐ *The lack of hemodynamic changes due to Tracrium suggests minimal histamine release*

Please see brief summary of prescribing information on the following page.

REFERENCES:

1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. Seminars in Anesthesia 1982; 1:57-62.
2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. Anesth Analg 1982; 61:730-734.
3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 1982; 61:723-729.
4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. Anesthesiology 1982;57:A261.

TRACRIUM® INJECTION
(atracurium besylate)

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TRACRIUM® INJECTION
(atracurium besylate)

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:

General: Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower, concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 2 years have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:

Musculoskeletal: Inadequate block, prolonged block

Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia

Respiratory: Dyspnea, bronchospasm, laryngospasm

Integumentary: Rash, urticaria, reaction at injection site

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

HOW SUPPLIED: Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).

10 ml Multiple Dose Vial (100 mg atracurium besylate per vial). The multiple dose vial contains 0.9% benzyl alcohol added as a preservative. Box of 10 (NDC-0081-0940-95).

Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

U.S. Patent No. 4179507 Printed in U.S.A.

Find out more about
TRACRIUM® INJECTION
(atracurium besylate)
at
The International Anesthesia Research Society Meeting

Las Vegas
March 15-19, 1986

TRACRIUM® INJECTION
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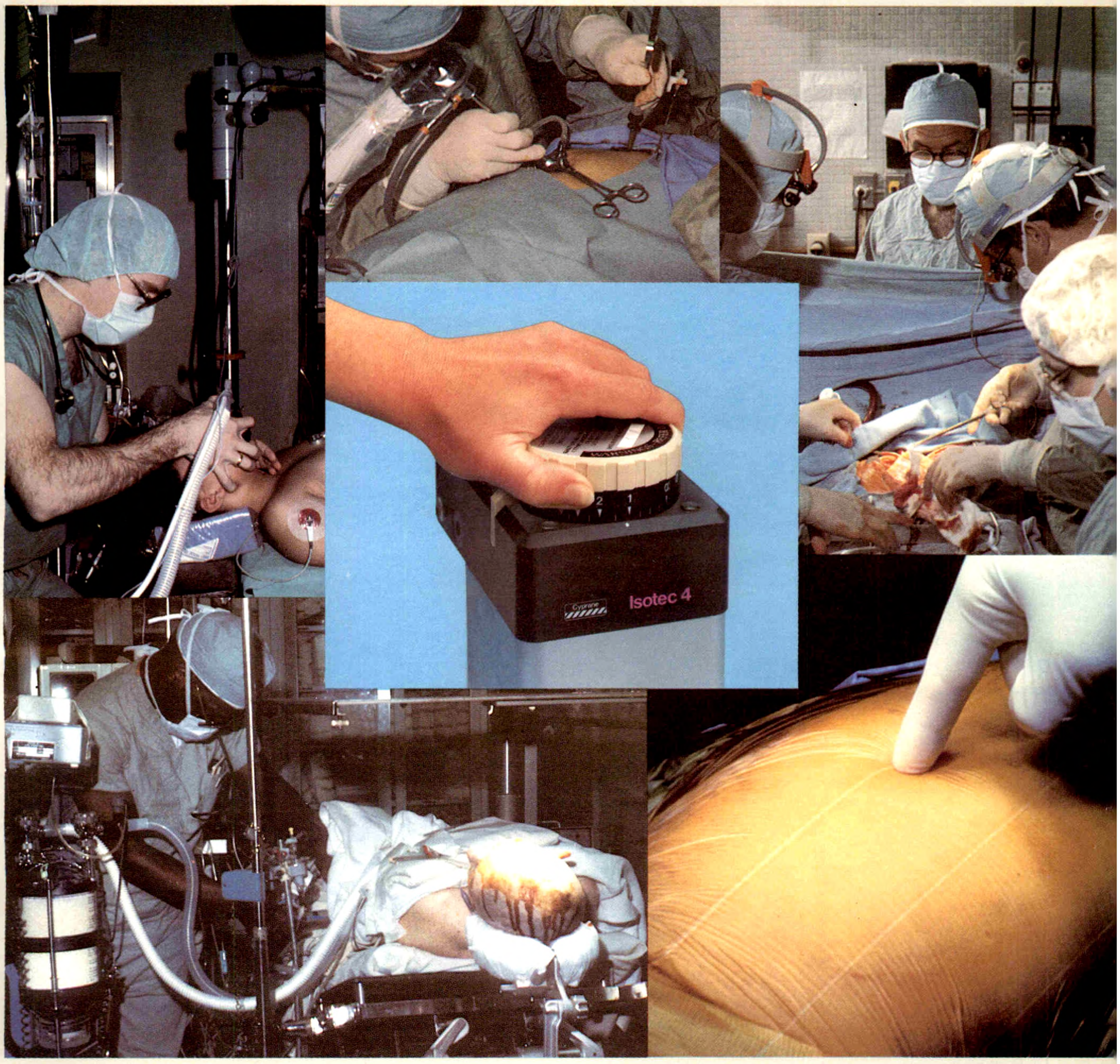
Forane® (isoflurane)
The Versatile Anesthetic



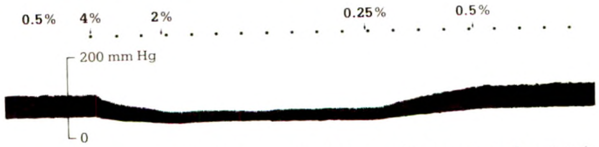
Anaquest

Forane® (isoflurane)

Forane® (isoflurane)
The Versatile Anesthetic

A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.[1]



Blood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.[1]

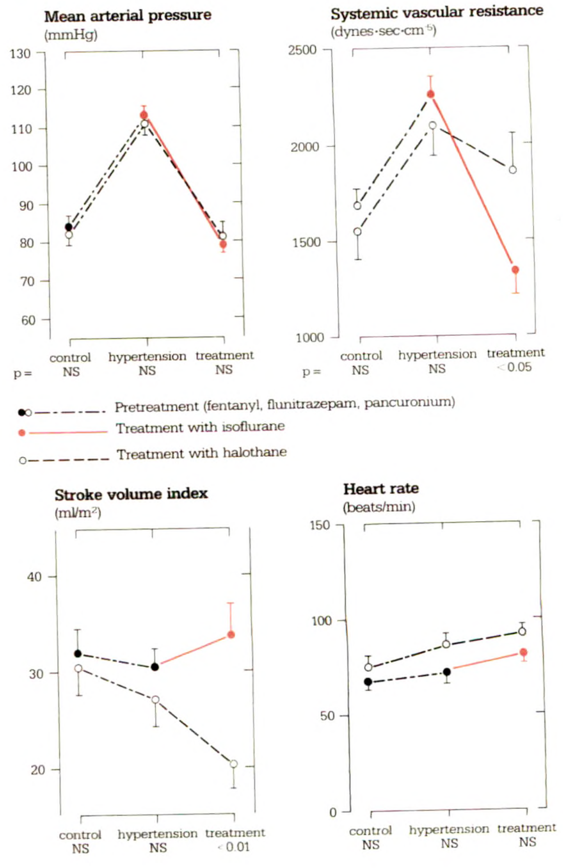
Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when $PaCO_2$ is controlled at 25-30 torr, and ICP may be readily lowered *during surgery* by decreasing $PaCO_2$.[2]

Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surgery (Adapted from Hess et al[3]).



Potentiation of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).[4,5] Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."[6]

A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."[7] (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.[8]

Post-laparoscopy Nausea (N) and Vomiting (V)

Group	No. of Patients	No. of Patients with N or N&V
fentanyl, N_2O, O_2	37	23 (62%)*
isoflurane, fentanyl, O_2	20	6 (30%)
isoflurane, O_2	20	5 (25%)

Adapted from Alexander et al[8] *$p<0.05$

References:

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742-748, 1983. 2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 54:97-99, 1981. 3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. Anesth Analg 62:15-20, 1983. 4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509-514, 1971. 5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709. 6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? Anesth Analg 60(9):666-682, 1981. 7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981. 8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. Anesth Analg 63:175, 1984.

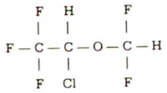
For complete use information, please see following page.

Forane® (isoflurane) **...a product of original Anaquest research**

Forane® ...The Versatile Anesthetic
(isoflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION: FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$F-\overset{\overset{F}{|}}{\underset{\underset{F}{|}}{C}}-\overset{\overset{H}{|}}{\underset{\underset{Cl}{|}}{C}}-O-\overset{\overset{F}{|}}{\underset{\underset{F}{|}}{C}}-H$$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where:} \quad \begin{aligned} A &= 8.056 \\ B &= -1664.58 \\ T &= °C + 273.16 \text{ (Kelvin)} \end{aligned}$$

Partition coefficients at 37 °C	
Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8
Partition coefficients at 25 °C - rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY: FORANE (isoflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE: FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS: Known sensitivity to FORANE (isoflurane) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS: Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS: General: As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O. See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS: Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION: Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\ P_V\ F_V}{F_T\ (P_A - P_V)}$$

where: P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED: FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0117

Revised 5-84

Anaquest Forane® (isoflurane)

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The successful applicant should have formal training beyond the 3-y continuum in a subspecialty of anesthesiology practice or have recognized skills in a subspeciality area of anesthesiology in lieu of formal fellowship training. Neuroanesthesiology, pain therapy, or cardiovascular anesthesia would be particularly desirable. The successful candidate must have a commitment to teaching medical students and residents in addition to his or her own clinical expertise. The ability and desire to do clinical and/or basic research is essential. Academic title and compensation will be consistent with experience. The Hitchcock Clinic and Dartmouth Medical School are EE/AAE. Send CV to David Glass, MD, Hitchcock Medical Center, 2 Maynard Street, Hanover, NH 03756.

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Course Directors:
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Our Visiting Professor is Dr. Gordon H. Bush, Consultant Paediatric Anaesthetist, Director of Anaesthesia, Alder Hey Children's Hospital, Liverpool, U.K.

The meeting comprises **three half-day teaching sessions**, allowing participants and their guests to take advantage of a variety of social, cultural, athletic, and shopping activities. The program is approved for 15 credit hours in category 1 of the Physician's Recognition Award of the AMA. Application has been submitted to the American Association of Nurse Anesthetists for continuing education credits to be awarded to nurse anesthetists completing this course.

For further details please contact Harvard Medical School, Department of Continuing Education, Boston MA 02115 (617-732-1525, M–F, 10 am–4 pm Eastern Time).

Course Directors: Drs. Charles J. Coté, Letty M. P. Liu, Nishan G. Goudsouzian, and John F. Ryan, Department of Anesthesia, Massachusetts General Hospital, Boston, Massachusetts.

NITROUS OXIDE/N_2O

Editor: **Edmond I. Eger II, M.D.,** Professor and Vice Chairman for Research, Department of Anesthesia, University of California, San Francisco

After 140 years of use, nitrous oxide is now known to be more than an inert vehicle for other, more potent anesthetics. Nitrous oxide affects the function of every body tissue significantly. Optimum application requires a full appreciation of both the benefits and potential hazards of this anesthetic substance.

Nitrous Oxide/N_2O is a complete resource on the subject. It describes what is known about nitrous oxide – applications and contraindications – and debates its continued clinical use. The current clinical applications of N_2O are reviewed by means of:

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- detailed summary of known side effects and toxicity
- practical guidelines for avoiding and managing these effects

Finally, the case for administering this anesthetic is carefully and candidly assessed in chapters by proponents of both views. ***Nitrous Oxide/N_2O*** is a controversial work that everyone using the drug will want to read.

Contents. Preface. Contributors. A History of Nitrous Oxide. Physics, Chemistry, and Manufacture of Nitrous Oxide. Nitrous Oxide Analgesia. MAC. Nitrous Oxide Delivery Systems. Pharmacokinetics. Respiratory Effects of Nitrous Oxide. Cardiovascular Effects of Nitrous Oxide. Central Nervous System Effects of Nitrous Oxide. Neuromuscular Effects of Nitrous Oxide. Nitrous Oxide in Obstetrics. Metabolism of Nitrous Oxide. Nitrous Oxide Inactivates Methionine Synthetase. Mutagenicity, Carcinogenicity, and Teratogenicity of Nitrous Oxide. Nitrous Oxide Abuse. Toxicity of Nitrous Oxide. The Use of Nitrous Oxide by Dentists. Nitrous Oxide in Veterinary Practice and Animal Research. Controlling Occupational Exposure to Nitrous Oxide. Should We Not Use Nitrous Oxide. We Should Continue to Use Nitrous Oxide. Epilogue. Index.

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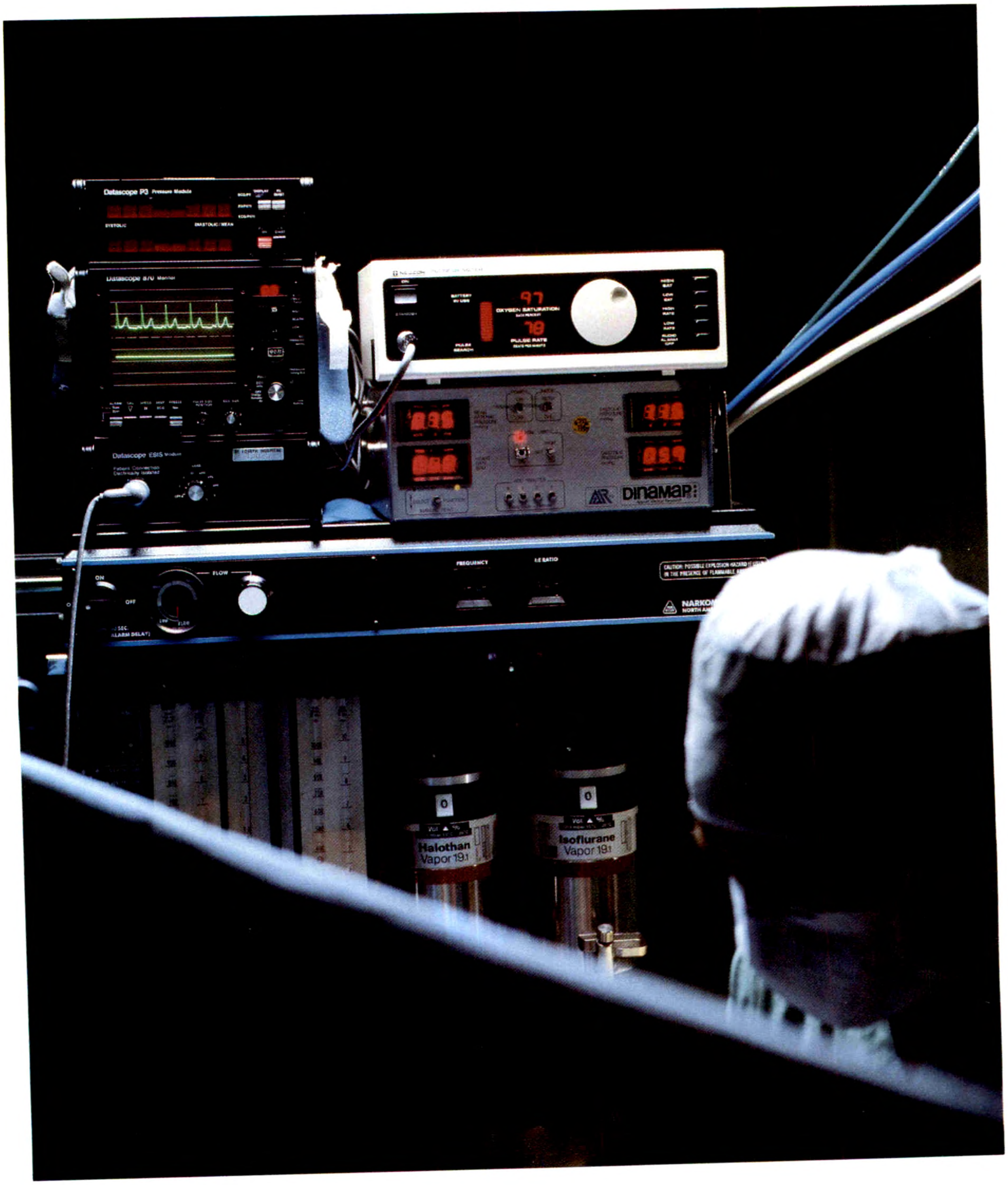

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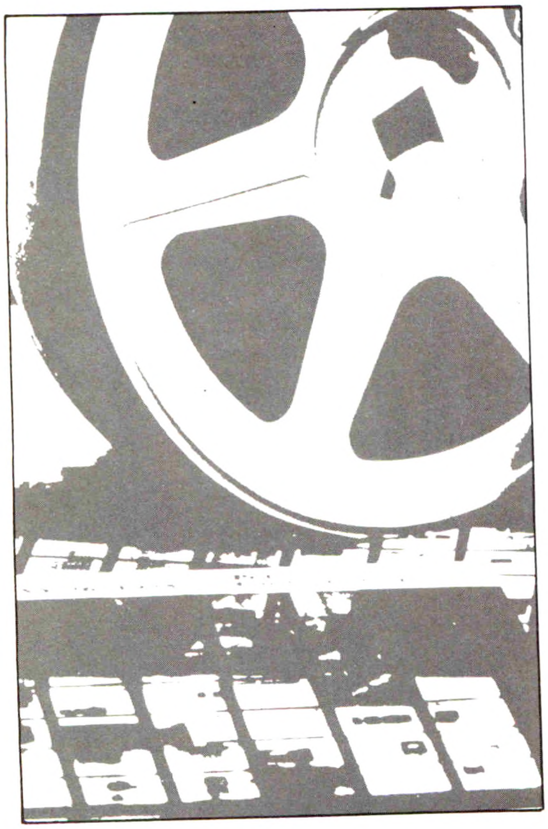

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ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

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